The staircase test of skilled reaching in mice

Alison L. Baird, Alicia Meldrum and Stephen B. Dunnett [1]

School of Biosciences, Cardiff University, Cardiff, Wales, UK.

[1] Address for correspondence:

Stephen B. Dunnett,

The Brain Repair Group,

School of Biosciences,

Cardiff University,

Museum Avenue, PO Box 911,

Cardiff CF10 3US, Wales, UK.

Tel: (+44) 2920 875188 / 875541

Fax: (+44) 2920 876749

E-mail: dunnett@cf.ac.uk

ABSTRACT

- 1 -

The 'staircase' test has become established for measurement of side-specific deficits in co-ordinated paw reaching in rats, and has been shown to reveal impairments on the contralateral side following unilateral lesions in a wide range of motor structures of the brain. As mice become more widely used in behavioural neuroscience, we have scaled down the staircase reaching test for application to this latter species. We here validate the test in C57BL/6J mice by (a) establishing the optimal dimensions of the apparatus, (b) comparing the effects of test parameters including sex, test duration, levels of deprivation and alternative reward pellets, and (c) demonstrating contralateral deficits after aspirative lesions of the motor cortex. Differences between mice and rats in normal performance of the task are noted. The staircase test provides a simple objective test of skilled motor function that allows measurement of lateralised effects without unduly constraining the animal, and which may prove as useful for mice as has previously been demonstrated in rats.

INTRODUCTION

Mice are increasingly used to study genetic factors in health and disease based on transgenic and targeted knock-out and knock-in strategies [26,45]. However, most behavioural analyses have been developed in rats, and sophisticated behavioural assessment for mice, whether based on comprehensive screening of neurological deficits or targeted assessment of specific functions, has until recently been lacking. This situation is now being rapidly addressed using different strategies of neurological screening to characterise new strains, mutations and transgenes [12,46]. Moreover, more detailed analyses, for example using operant techniques, can discriminate specific aspects of complex function [27,33].

Motor deficits are a common feature of neurological mutants and transgenic mice, and so have to be evaluated prior to any other level of analysis [3,7,30,39]. Most motor testing for mice has been based on descriptions of behaviour in open fields [10,13,30] or on co-ordination and balance on tasks such as the rotarod and raised beam [7,29,31]. However, observation of mice confirms that they, as in other rodent species, have considerable manipulative ability, most obviously seen when climbing or when picking up pieces of food to investigate or eat.

In order to test manipulative skills, a variety of tasks have been developed for rats based on reaching for food, configuring the apparatus so as to require the animals to make explicit reach and grasp movements to pick up and retrieve food pellets. One of these, the 'staircase' test, was introduced for rats in 1990 by Montoya and colleagues [1,35,36] and has subsequently been shown to be sensitive to detect unilateral lesions in motor cortex [36], striatum [20], nigrostriatal bundle [2,5,52], subthalamic nucleus [25], pedunculopontine tegmental nucleus [15] or ischaemia [22,32] and the restorative effects of neuroprotection [4,14,18,47] or neuronal grafts [2,21,35,37,38]. We have therefore sought to scale down the rat staircase apparatus to be applicable to mice. We here provide a first report of the viability

of this test for mice, we establish the importance of various test parameters such as session length, level of deprivation, and composition of the food pellets used as rewards, and we validate the test by confirming a selective contralateral reaching deficit after unilateral lesion of the motor cortex.

MATERIALS AND METHODS

Subjects

Young adult mice of the C57BL/6J strain of both sexes (male n=6, females n=5) were obtained from a commercial animal breeder (Charles River, Sittingborne, Kent) at 6 weeks of age. The mice were caged in same-sex pairs in an animal colony maintained on a 12h : 12h regular light-dark cycle. During periods of experimental testing, the mice were kept on a 20h food deprivation regime (other than when specified otherwise, below) and fed on a standard lab chow diet at the end of the test sessions that took place 11.00 -13.00 daily. Water was available *ad libitum*.

Apparatus

The test apparatus was based on the design previously published for rats [1,36] scaled down for mice, and is illustrated in Fig 1. Briefly, the test apparatus comprises a start compartment with hinged lid. A narrow corridor extends horizontally from one wall of the start compartment. A central plinth runs the full length of the corridor with a narrow trough on either side, into which can be inserted a removable double 'staircase' with 8 steps on each side. A shallow well is drilled in the centre of each step into which can be placed food pellet rewards. The dimensions of the corridor, plinth, troughs and steps are such that a mouse can climb onto the plinth, and can reach down on either side to grasp and retrieve food pellets

from the steps of the left staircase with its left paw and from the steps of the right staircase with its right paw. The width is such that the mouse cannot turn round in the corridor (and hence cannot use the opposite paws to retrieve pellets) and can only exit from the corridor backwards. Boxes were custom built in the mechanical workshop of Addenbrooke's Hospital, Cambridge (now available commercially from Campden Instruments, UK, and Lafayette Instruments, USA). All tests were conducted in a bank of 6 boxes allowing all mice of the same sex to be tested simultaneously. The boxes were positioned on an open bench with standard overhead artificial fluorescent strip lighting in the room. Mice were tested and trained using BioServ 20 mg sucrose reward pellets, other than in the explicit comparison of alternative diets, described below.

Training

Mice were food deprived on a 20 h food deprivation regime. They had access to standard lab chow for 4h daily, given immediately after the daily test session or from 12.00 on non-testing days. At the outset of testing the mice were first familiarised to the food pellets by placing approx. 50 into each home cage on three consecutive days. They are then familiarised to the test boxes by placing food pellets along the surface of the central trough as well as on the staircase steps for a further two days. On subsequent days, the double staircase was baited with 2 pellets per step (16 on each side, total 32 pellets per test box) and the mouse was placed in the start compartment. During training, each test session lasted for 15 min, at the end of which the numbers of pellets remaining on each step and knocked down to the floor were counted.

From the raw data, two experimental variables were calculated for each side:

Number of pellets collected. The number of pellets retrieved on each side of the staircase, (i.e., 16 minus the number of pellets remaining).

Maximum distance reached. The lowest step (numbered 1 … 8 from the top) with <2 pellets remaining, i.e. from which at least one pellet had been displaced.

All mice were trained daily for 15 days, prior to introducing variations of the test parameters.

Test parameters

Session length. Over 8 test days, the session length was alternatively 5, 15, 30 or 60 min duration, in a Latin square counterbalanced order between mice.

Deprivation. The level of food deprivation was varied over 6 days, with the daily food removed 1, 6 or 20 h prior to testing, each on two consecutive days, in counterbalanced order between mice. Performance was measured only on the second test day at each level of deprivation.

Reward diet. Five different food pellet preparations were compared, in each case delivered as 20 mg pellets obtained commercially, with sucrose, banana, chocolate or grain flavours (BioServ) or grain diet (Noyes). All feeds were first given in the home cage to reduce neophobia, then each mouse was tested twice on each diet in counterbalanced order over 10 days.

Cortical lesions

In a final stage of the experiment, all animals were returned to free feeding for 1 week prior to receiving unilateral lesions in the right frontoparietal cortex. The mice were anaesthetised with halothane in a 2 parts oxygen 1 part nitrous oxide mixture and mounted in a stereotaxic frame. Following a midline incision in the scalp, a bone flap was removed from approx. 1-3 mm lateral of midline and from approx. 1 mm posterior - 2 mm anterior to bregma to expose the dura. The dura was incised with a cross cut using a #11 scalpel and an approx.

2x2 mm area of superficial cortex was aspirated using a 19 gauge dome tipped needle on a hand-piece with finger-regulated vent attached to an Aesculap suction pump. The wound was plugged with Spongostan foam (Ferrisan, Denmark) soaked in sterile saline and sutured. The mice required no special post operative care but were administered Temgesic analgesia via the water supply for 48 h following surgery. One week after surgery, the food deprivation regime was reintroduced and mice were tested on 9 further sessions in the staircase apparatus, undertaken in 3 day blocks 1, 2 and 3 weeks after lesion.

Histology

Upon completion of behavioural testing, mice were deeply anaesthetised with 0.2 ml Euthatal i.p. and perfused through the heart with approx. 25 ml sterile saline followed by 50 ml 4% paraformaldehyde in phosphate buffered saline. The brains were removed from the skulls and post fixed in 20% sucrose. The whole brains were photographed from a dorsal perspective with a digital camera and then sectioned at 40 µm on a freezing sledge microtome, mounted and Nissl stained with cresyl violet for mapping of lesions and photomicroscopy in coronal sections.

RESULTS

Training.

All mice learned to collect pellets from the staircase within the first couple of days of testing. However, the numbers of pellets retrieved improved with practice. In early sessions many pellets were knocked down and accumulated on the floor of the trough, whereas with repeated training performance improved and more pellets were retrieved (and presumably eaten) during the later training sessions. By the end of training mice were retrieving

approximately 8 pellets per side (6-10 depending on the individual animal). There were no marked side differences, so that any one animal performed similarly between the two sides and variability of performance occurred between animals rather than between sides; there was no overall difference in performance between the two sexes.

Observations of how the mice actually performed the test indicated one major difference from previous descriptions in rats. Whereas a rat will climb onto the central plinth, and reach, retrieve and eat a series of pellets in rapid succession, mice more typically retrieve one pellet at a time, and back out of the corridor carrying the pellet in its mouth, to eat it in the start chamber. The mouse then returns to the corridor to collect and retrieve another pellet for consumption back in the start chamber. Consequently, mice take longer to eat a given number of pellets than rats, which may influence the selection of an appropriate session length required to monitor the limits of performance capabilities (see below).

Session length

On the basis of observations of the way mice retrieved and ate pellets singly, we first assessed whether session duration influences performance. As shown in Fig 2A,B mice typically cleared 2 steps and retrieved 3 pellets on each side within a 5 min session, cleared and retrieved about double this number of pellets within 15 min and did not reach an asymptote of performance, clearing 5-6 steps and retrieving 6-10 pellets until they had been allowed 30 min in the test boxes. Performance was similar for the longest session length; the mice did not retrieve any more pellets when allowed a further 30 min in the test boxes. The effect of session length was highly significant on both measures (pellets collected, $F(1,9) = 32.53$; max distance reached, $F(1,9) = 47.04$; both $p<0.001$), whereas no other effects or interactions of Sex or Side were significant.

In view of these results, all further tests were conducted with sessions of 30 min duration.

Deprivation level

Mice appeared to work vigorously for palatable sucrose flavoured pellets, even when food deprived for a duration less that we would typically use in rats. The mice were therefore tested under three levels of food deprivation. As shown in Fig 2C,D there was only a very slight decline in either measure of performance as the level of deprivation was reduced from 20 h to 1 h, and this difference was not significant (pellets collected, $F(1,9) = 1.57$; max distance reached, $F(1,9) = 2.01$; both $p>0.15$).

Reward diet

Since trained mice worked vigorously to retrieve pellets even when under only modest levels of deprivation we assessed whether the palatability of the rewards, as reflected by using diet preparations of different compositions and flavours would influence performance. As shown in Figure 2D,F, there were small but consistent and significant differences between the preparations, with the BioServ chocolate, banana and grain being most favoured and the Noyes grain diet the least (pellets collected, $F(1,9) = 12.17$; max distance reached, $F(1,9) = 14.68$; both $p<0.001$).

Cortical lesions

All mice recovered rapidly from cortical lesion surgery although two animals died under subsequent anaesthesia to replace lost sutures on the following day.

All remaining animals were sacrificed for histology upon completion of 3 weeks of testing after lesion surgery. As illustrated in Fig. 3, the lesions in these 9 mice were relatively similar in extent and removed the dorsal motor area (including snout and forelimb representations [23]) in all animals.

The lesions significantly disrupted the number of pellets collected with the contralateral but not the ipsilateral paw (Fig. 4A; Side, $F(1,7) = 7.46$, $p< 0.05$), and this effect was similar between male and female mice and at all three time points post surgery (Sex, $F(1,7) = 0.91$; Weeks, $F(2,14) = 1.96$; both $p>0.15$). By contrast to the number of pellets collected, the maximum distance reached did not differ between the two sides (Fig. 4B; Side, $F(1,7) = 1.15$, $p>0.3$) but did decline progressively over consecutive weeks of testing (Weeks, $F(2,14) = 6.31$; both $p<0.05$).

DISCUSSION

Although a variety of tests of skilled reaching have been developed for rats ? based on reaching through bars, into tubes, down staircases or pressing levers [1,5,6,19,24,34,35,41,43,48,50] ? there has been (with very few exceptions [49]) little attention given to skilled motor performance in mice. With recent advances in powerful molecular tools for genetic manipulation in mice, not least based on transgenic, knock-out and selective knock-in strategies to complement conventional mutation approaches, the need to develop sensitive behavioural screens is receiving a new urgency [12]. At present, most tests of motor function for mice are based on measures of locomotor activity in activity cages and open fields [11,13,46] or of balance in tests such as rotorod and beam balance [8,9,46]. Although these require motor co-ordination they do not challenge the manipulation skills using individual paws of which rodents are conspicuously capable.

As in rats, a test of skilled motor co-ordination may be provided by tasks involving paw reaching for food. To this end, Whishaw has employed kinematic analysis of mice reaching into slots or through vertical bars to retrieve food pellets to show that mice exhibit a similar degree of motor control and similar profiles of action to that seen in rats [49]. In an attempt to

provide an alternative task that provides objective measures of performance without requiring continuous monitoring and observational ratings of the animals, we have now adapted the rat staircase test to mice. First introduced for rats by Montoya and colleagues in 1990 [35,36], the staircase has two favourable features as a test of skilled forelimb reaching. First, it provides a simple objective measure rather than depending on observational rating of performance. Whereas careful observational analysis will always be required for the most detailed descriptions of reaching performance [49,50,52], direct observation and rating is very time consuming and potentially subject to observer biases. By contrast, the staircase test provides an objective measure of performance, which is efficient to administer, allows testing of multiple animals in parallel without extensive technician training nor need for validation of inter-rater reliability [1,36]. Second, the staircase test provides separate measures of performance for the left and right forelimbs without the requirement to restrict use to one limb at a time, for example by bandaging or injection with anaesthetic [16,17,24,50]. This is achieved by judicious configuration of the apparatus that does not allow the animals to adapt postures which enable them to use the unaffected paw even on the supposed affected side [1], a problem that has confounded many previous attempts to devise measures of lateralised performance based on reaching into tubes [41,42].

The present test boxes are based on a series of pilot constructions varying the test apparatus to establish dimensions in which mice will readily enter the corridor, mount the plinth and work to retrieve food pellets, but are sufficiently constrained not to be able to turn round. We also varied the depths of the steps of the staircases in order to establish an optimal level that produced intermediate performance in normal mice without reaching floor or ceiling levels with various levels of training and behavioural, surgical or pharmacological manipulation. The present set of dimensions and parameters have now been adopted for

validation and experimental use, the first stage of which is undertaken in the present experiment.

First, we can affirm, with Whishaw [49], that mice are fully capable of co-ordinated independent limb use that is reliably quantifiable in the test apparatus. Secondly, young adult mice will learn to perform to relatively stable (asymptotic) levels of performance over about 15 days of training. We recommend several weeks of training, rather than simply a few days, in order to establish a stable baseline before applying, and against which to measure, any experimental surgical or pharmacological manipulation. We found rather similar performance of male and female mice in all our tests, and in no case were significant Sex differences noted ? although it should be noted these were based on rather small group sizes within which small or subtle sex differences would not be detectable.

Although the kinetics of reaching may be similar between the two commonly used rodent species [49], we observed that the overall behavioural strategy adopted by mice differs from that seen in rats. Whereas rats typically will work at retrieving and eating pellets while remaining positioned on the plinth, mice retrieve one pellet at a time and retire to the start box to eat it. As a consequence, mice take longer to clear all pellets within their reach, and they require a full 30 min tests to produce asymptotic performance, in contrast to the 10-15 min we have previously found sufficient for rats in a similar apparatus [1,35]. Also, we found that well trained mice were less sensitive than expected from previous work with rats to acute variations in deprivation but were similarly sensitive to variations in dietary composition of the reward pellets. Attention therefore needs to be given to the choice of type and source of reward pellets based on a combination of factors including palatability, availability and ease of storage.

We have not (yet) evaluated whether there are significant differences between different ages or strains of mice, but many studies in other behavioural paradigms would lead us to

expect that such differences may well be important [12,13,28], and both of these dimensions clearly now warrant further study. However, by way of validation of the task, we have confirmed that unilateral lesions of the motor cortex in mice induce deficits in reaching with the contralateral paw, similar to previous reports in rats [36,42,44,51]. Of particular interest was the observation that the mice showed a significant contralateral deficit in the measure involving the numbers of pellets successfully retrieved, but not in the maximum distance reached. This suggests that the deficit was indeed an impairment in motor skill rather than of a contralateral neglect or a reduction in the attempts on that side, since the mice are stretching as far on the affected as on the intact side. Conversely, the maximum distance reached showed a small but significant decline with repeated testing, which may have been related to a decline in motivation associated with impaired performance (somewhat akin to the phenomenon of learned helplessness [40]) but this also requires further studies to resolve properly.

In summary, the staircase test provides a simple, objective measure of skilled reaching in mice that allows easy quantitative identification of lateralised deficits without recourse to limb restraint. As in rats, the staircase test may be of use to evaluate deficits and recovery of skilled motor performance in mice subject to a variety of behavioural, developmental, surgical, pharmacological or genetic manipulations.

FIG. 1. A. Photographs of two staircase test boxes for mice. Note the rear box has an unbaited staircase in position, the front box has the staircase removed and the right hand flight of stairs baited with 2 x 20 mg sucrose pellets per step. **B.** Schematic illustrations, from three orthogonal perspectives, of the test apparatus with start box, corridor and central plinth, and critical dimensions indicated (in mm). Placement of the double staircase when inserted is indicated by dashed outline. **C.** Orthogonal perspectives and critical dimensions of the removable double staircase.

FIG. 2. Effect of test variables on performance. **A,B.** Session length, varied between 5 and 60 min. **C,D.** Level of food deprivation, with testing conducted 1, 6 or 20 h after food was removed. 20h is the standard level of deprivation used throughout training, with the reduced levels of deprivation applied in counterbalanced order during these particular trials only. **E,F.** Reward pellets composed of five alternative diets, in each case administered in the form of 20 mg pellets. For each variable, performance was measured both as the numbers of pellets collected (**A,C,E**) and as the maximum distance reached (**B,D,F**). Data for male and female rats are presented separately in each case; results did not differ between the two sides in any case and are presented combined. Vertical bars indicate means $\pm$ sem. Asterisks indicate significant differences ($p<0.05$) between groups.

FIG. 3. Cortical lesions in the right frontoparietal motor cortex. **A.** Photograph of the dorsal surface of one case of a whole perfused brain. The borders of the aspirative lesion in the right frontal cortex are indicated by arrow heads.. **B.** Outlines of the extent of damage at the level of the cortical surface in each of the 9 cases analysed. **C,D.** Photomicrographs of lesions in

motor cortex illustrated at middle and more caudal levels from two different cases. Note that whereas the extent of damage at the surface is rather similar, the extent of the lesions can differ at deeper levels. Scale bars = 1 mm in each case.

FIG. 4. Unilateral lesions of motor cortex induce modest but significant deficits in reaching on the contralateral side. Note that the maximum distance of reaching (**A**) is comparable on the two sides but the mice retrieved fewer pellets with the contralateral paw (**B**), suggesting that the deficit was one of lateralised motor inco-ordination rather than of motivation or contralateral neglect. Asterisks indicate significant differences ($p < 0.05$) between sides

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