Measuring cognitive deficits in disabled mice using an automated interactive touchscreen system

To the editor: The concomitant appearance of motor disability and cognitive deficits is very common in neurodegenerative disease[1]. Although progress in developing valuable mouse models for these diseases has been excellent, there are few cognitive tests suitable for animals with motor impairments. To tackle this problem, we used an automated touchscreen-based cognitive-testing system[2] that can be used to test mice with motor impairments.

R6/2 mice have a rapidly deteriorating phenotype that has made them a popular model for Huntington disease research[3,4], but their severe motor phenotype[4] makes it difficult to test their cognitive function. We devised a two-choice visual discrimination task to test cognitive function in R6/2 mice (**Supplementary Methods** online). We presented pairs of stimuli (one correct, one incorrect) on a touchscreen. Two cohorts of mice learned to respond by 'nose-poking' the screen (**Fig. 1a**,**b**) and collecting reward pellets for correct responses. We tested one cohort daily at 9–16 weeks of age and the other at 11–14 weeks of age.

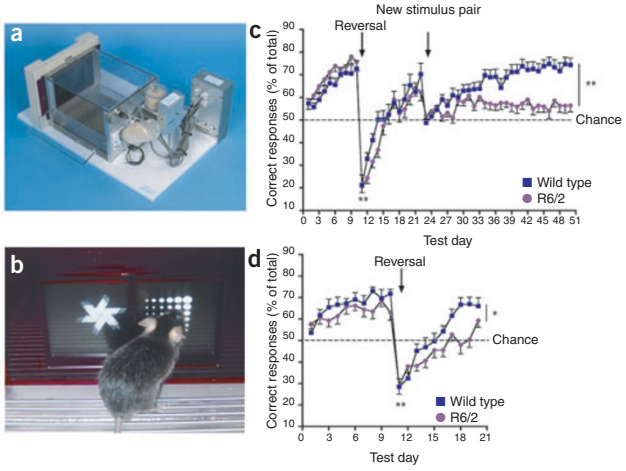

Figure 1 | Cognitive deficits in a two-choice discrimination task are detected in R6/2 mice using an interactive touchscreen system. (**a**,**b**) The touchscreen apparatus. (**c**,**d**) Two cohorts of wild-type and R6/2 mice were tested for 10 d. On day 11 the S+ (correct stimuli) and S– (incorrect stimuli) were reversed. After completion of the reversal phase, the younger cohort (**c**) was given a new S+ and S– and tested for an additonal 14 d. Mean performance on each day (±s.e.m.) is shown. In **c**, $n = 25$ for wild-type and $n = 22$ for R6/2 mice. In **d**, $n = 11$ for wild-type and $n = 15$ for R6/2 mice. $^{*}P < 0.05$, $^{**}P < 0.001$.

Mice learned to discriminate between the stimuli within 10 d (**Fig. 1c**,**d**). On day 11 we reversed the task, so the previously correct stimulus was now incorrect. On the first day of reversal, all mice showed a significant ($P < 0.001$) decrease in correct choices, as they continued to choose the previously correct stimulus. After that, wild-type and R6/2 mice in the younger cohort began to learn the reversal, and by day 22 they had learned the task (**Fig. 1c**). Older R6/2 mice, however, showed significant impairments in reversal learning ($P < 0.05$; **Fig. 1d**).

At the end of reversal testing, we presented mice in the younger cohort with a new pair of stimuli (**Fig. 1c**). In contrast to wild-type mice, R6/2 mice were unable to learn the new discrimination. Notably, although 16-week-old R6/2 mice failed to learn the task, they still completed all the trials, indicating that cognitive impairments were not secondary to motor impairments, and motor-impaired mice can perform well in this apparatus.

The learning deficits shown here are similar to acquisition and reversal deficits we described previously in water-based paradigms[5,6], but there are major advantages to using this system. First, the task is physically undemanding, so mice do not become fatigued. Second, it uses rewarding, not aversive stimuli, so it is not stressful. Third, it is directly comparable to touchscreen tasks used to test humans. Finally, it is less labor-intensive than traditional cognitive testing. With 12 boxes, it takes about 2 h of operator time per day to run the task for 64 mice, compared with the 8 h needed to test that number of mice in the two-choice swim tank.

The touchscreen system will be invaluable for testing cognition in animals with neurological dysfunction, particularly where motor deficits make cognitive testing difficult or impractical.

Note: Supplementary information is available on the Nature Methods website.

ACKNOWLEDGMENTS

This work was supported by a grant from the HighQ Foundation.

A Jennifer Morton[1], Elizabeth Skillings[1], Timothy J Bussey[2] & Lisa M Saksida[2]

Departments of Pharmacology[1] and Experimental Psychology[2], University of Cambridge, Cambridge CB2 1PD, UK.
e-mail: ajm41@cam.ac.uk

1. Donaghy, M., ed. *Brain's Diseases of the Nervous System* 11th edn. (Oxford University Press, Oxford, 2001).
2. Bussey T.J. *et al. Behav. Neurosci.* **115**, 957–960 (2001).
3. Beal, M.F. & Ferrante, R.J. *Nat. Rev. Neurosci.* **5**, 373–384 (2004).
4. Carter, R.J. *et al. J. Neurosci.* **19**, 3248–3257 (1999).
5. Lione, L.A. *et al. J. Neurosci.* **19**, 10428–10437 (1999).
6. Morton, A.J. *et al. Eur. J. Neurosci.* **21**, 855–870 (2005).