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Research report

Selective cognitive impairment in the YAC128 Huntington's disease mouse

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ABSTRACT

People with HD have a demonstrated early extra-dimensional set-shifting deficit. In the present study, we use a novel water T-maze set-shifting procedure and demonstrate its validity as a set-shifting task in a mouse model of Huntington's disease. Three groups of YAC128 mice of different ages (27, 69 and 117 weeks) were run on the task, which incorporated six distinct stages in which the mice must learn a rule and then switch to a different rule. The six stages were: directional learning, directional learning reversal, light discrimination, light discrimination reversal, return to place learning and a maze rotation spatial learning test. Rule changes from place learning to light discrimination and back constitute extra-dimensional shifts. The results of the study demonstrate robust light/dark discrimination reversal learning deficits in transgenic mice from 27 weeks of age, and a directional learning to light discrimination extra-dimensional set-shifting deficit from 69 weeks of age. The extra-dimensional shift deficit was confirmed with control trials demonstrating the validity of the deficit and the task. The onset of reversal learning and extra-dimensional shift deficits corresponded with the development of mutant huntingtin N-terminal fragment aggregates in neurons of relevant forebrain regions.

1. Introduction

Huntington's disease (HD) is caused by an expanded CAG mutation in the Hdh gene [47] that results in the production of the mutant huntingtin protein. For unknown reasons, abnormal cleavage of the mutant protein leads to protein aggregation and nuclear depositions of N-terminal protein fragments within neurons [14]. At present it is unclear what the precise role of these inclusions is, but the huntingtin mutation ultimately delivers a toxic gain of function resulting in neurodegeneration and the broad array of symptoms in the sufferer. The neuronal populations most affected are the medium spiny neurons of the striatum and the pyramidal neurons of the cortex [53] and it is this cell loss that is regarded as the principal cause of the motor, cognitive and emotional abnormalities that characterise the disease [3].

The cognitive symptoms in patients may be highly specific in nature and include deficits in semantic verbal fluency and working memory, sequence learning, implicit learning and extra-dimensional (ED) set-shifting, and psychomotor performance, all of which have been identified in people during the early stages of the disease [19,21,24,27,30,31,46]. As the disease progresses the range of cognitive dysfunction broadens and can include deficits in pattern and spatial recognition, matching to sample, visual discrimination and its reversal, and sequential planning tasks, as well as specific attentional tasks [9,28,39]. However, the pattern and onset age of cognitive dysfunction can vary greatly between individuals. In neuroanatomical terms, many of these deficits represent fronto-striatal dysfunction. Since HD is caused by a single gene mutation it is an ideal candidate for the development of genetic models of the disorder of which several have been created in rodents [22,32,34,37,43,45,52,54]. Whilst all of these models demonstrate the cellular neuropathology of HD, if they are to be considered to be good models of the disorder they should ideally demonstrate some of the cardinal features of the fronto-striatal mediated behavioural pathology.

The YAC128 mouse is a transgenic model of HD with a full-length human gene with 128 CAG repeats inserted into the genome via a yeast artificial chromosome [45]. Originally this mouse line was maintained on an FVB/N background strain but has been subsequently backcrossed onto a C57BL6/J background [49]. Since FVB/N mice have a severe retinal degeneration, the C57BL6/J strain is preferable for behavioural testing, although there is evidence that the disease may be less penetrant on this background [49]. Nevertheless these animals have been demonstrated to have marked behavioural and anatomical abnormalities similar to those within the human condition. In general, the YAC128 mice have been shown to display motor and cognitive abnormalities including reversal learning deficits [45,51] formation of nuclear inclusions, as well

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as brain atrophy and striatal cell loss [50], but relatively little behavioural research has been conducted on the C57BL6/J variant.

To gain maximum benefit from the mouse models, the early identification of behavioural phenotypes is important for the outcome of therapeutic trials. An early deficit provides an opportunity for earlier intervention and a robust behavioural baseline provides a stable readout with which to assess the efficacy of that intervention. These can only be achieved if the test being used is sufficiently sensitive to the specific deficit under investigation. Thus, behavioural tests should probe for the functional impairment expected from the neuropathology of the target model. We have previously demonstrated ED shift deficits in the Hdh$^{(CAG)150}$ HD mouse line [7] using a set-shifting task designed by Birrell and Brown [4]. Similarly, reversal learning deficits have been demonstrated in the R6/2 and YAC128 mouse lines [33,51]. Whilst our previous [7] study successfully demonstrated a behavioural deficit in the Hdh$^{(CAG)150}$ mice, subsequent attempts to use the task on mouse lines with different genetic constructs and different background strains have proved difficult for a number of reasons (discussed below). In taking account of all of these factors, we have developed a novel set-shifting procedure that utilizes a water T-maze to present a series of rule learning manipulations with which to probe the cognitive functions of the YAC128 (C57BL6/J) mouse line.

In our implementation, this task incorporates 2 ED shifts and 2 reversal shifts, which the animal must learn in order to efficiently find a submerged platform in the maze, although other shifts in learning are readily incorporated. As a control measure, an added maze rotation manipulation had also been incorporated in the task protocol to identify if the mouse groups are solving the directional aspect of protocol using different strategies (S-R or spatial) that may confound the interpretation of the experimental results. The aim of the present study was to validate the water T-maze task as a useful and robust task with which to probe set-shifting deficits in rodents, and then evaluate set-shifting deficits in the YAC128 mice across several ages.

2. Materials and methods

2.1. Subjects

The YAC128 mice express human full-length mutant htt with 128 CAG repeats inserted in to the mouse genome via a yeast artificial chromosome. All mice were bred in-house on a C57BL/6J background (after 10 plus generations of backcrossing onto this background from the original FVB/N stock). To determine genotype, mice were tail tipped under local anaesthetic and the tips preserved in ice and shipped for commercial processing (Laragen Inc., Los Angeles). For the main experiments 51 mice were used, 26 wildtypes and 25 carriers. These were divided across the age groups as follows: 27-week-old group consisted of 10 YAC128 mice, and 9 wildtype mice (n = 19 in total); the 69-week-old group consisted of 8 YAC128 mice, and 8 wildtype mice (n = 16 in total); the 117-week-old group consisted of 8 YAC128 mice, and 8 wildtype mice (n = 16 in total), of these 29 were female and 22 were male, (12 female and 11 male wildtypes with the remaining mice being transgenic). During experimentation 1 aged wildtype mouse and 1 aged transgenic mouse were found dead in their home cages. In the supplementary control experiment, a further group of old animals was used for control trials at 121 weeks of age (comprising 8 YAC128 mice, and 7 wildtype mice, n = 15 in total). Mice were housed in standard laboratory cages under normal 12 h light/dark cycle (lights on 06:30: off 18:30) in temperature (21 ± 1 °C) and humidity controlled rooms. The mice had free access to food and water. All experiments were conducted between 09:00 and 14:00 and were run in accordance with the United Kingdom Animals (Scientific Procedures) Act of 1986, and local ethical review.

2.2. Behavioural apparatus

The water T-maze apparatus (see Fig. 1A) was constructed of clear Perspex. All arms were 30 cm high and 7 cm wide, the stem 21.5 cm long and the two perpendicular side arms each 37 cm long. The apparatus was filled with water at 23 ± 2 °C to a depth of 22.5 cm. An escape platform could be placed at the end of either side arm (6 × 6 × 21.5 cm high), coloured white, and designed to sit snugly in to the arm of the maze at 1 cm below the water surface. The water was coloured white with pasteurised milk so as to make the platform invisible within the maze. Exterior to the maze, two standard angle poise lamps fitted with 40 W bulbs, were positioned to illuminate overhead the end of either arm. The lamps were raised above the height

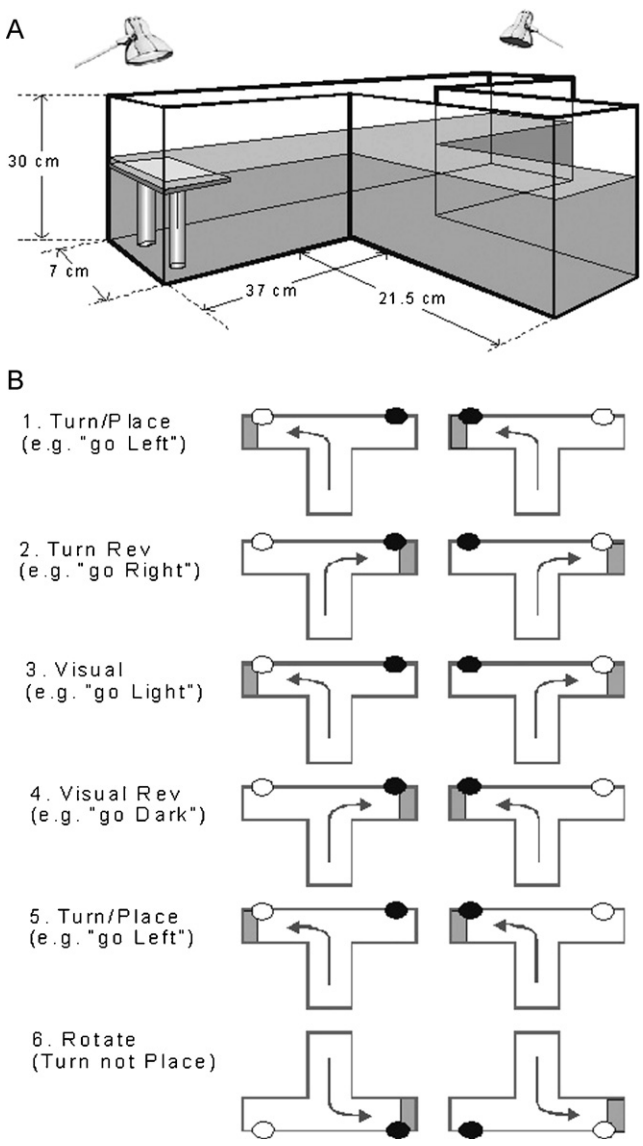

Fig. 1. Water T-maze set-shifting apparatus (A) and protocol (B) showing the six stages of the task. The task incorporates two ED shifts (stages 3 and stage 5), and two reversal shifts (stage 2 and stage 4). The final stage of the experiment (stage 6) is a maze rotation manipulation where the mice are probed for the different learning strategies.

of the maze and shone down into the water to produce a focused area of light close to the end of the respective arms. At any one time only one of the lamps was turned on. In addition to the lamps, extra-maze visual cues in the form of monochrome patterned posters were placed on the room walls adjacent to the apparatus. Whilst the only illumination in the test room came from the lamps, the external cues were clearly visible.

2.3. Behavioural task

The mice were tested successively, on a series of visual and directional discrimination tasks. In each case, training continued over several days until they reached criterion (see below), when they were then switched to the next task in the series.

Each animal was run 12 trials per day. The mice of each cohort were tested in rotation, such that each mouse was dried and returned to its home cage after each trial, and with an inter-trial interval of approximately 15 min. On each trial, the response choice was determined when the animals' body (excluding the tail) fully entered the arm. If the choice was correct (entering the arm containing the escape platform) the mouse was allowed to swim to and climb onto the platform, and was removed after 5 s. If the animal performed an incorrect choice, the animal was constrained to swim in the incorrect arm for 10 s, using a plastic blocking panel that fitted precisely to the width of the maze. All training employed a correction procedure whereby after 10 s the blocking panel was turned through 90° to open the