Impairment in reversal learning in a simple visual discrimination task in two mouse models of Huntington’s disease

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Abstract

Huntington's Disease (HD) is a neurodegenerative illness that is not only characterized by severe motor deficits but also by early cognitive deficits that significantly increase the burden for patients and caregivers. Considerable efforts have been concentrated, therefore, in the assessment of cognitive deficits in HD mouse models. Both the BAC (Bacterial Artificial Chromosome) transgenic mouse model, which expresses the full length human huntingtin (htt) transgene, and the z_Q175 knock-in mouse model show progressively impaired motor function in the rotarod, climbing and open field assays. In the present study, we tested 2 independent cohorts of z_Q175 KI mice (C57Bl6/J) and 2 independent cohorts of BAC transgenic mice, in an operant touchscreen assay in an effort to evaluate the line for deficits in the cognitive domain.

Methods

Subjects: BAC HD mice, carrying a 97 stable CAGCA repeats on a C57Bl6 x FVB/N F1 background (CHDI-007-3X11) were bred at the Jackson Laboratory (Bar Harbor, ME) and shipped to our facility and pair-housed as adults. 2, Q175 mice were bred at Psychogenics, Inc. WT mice reduced to 85% of their ad libitum body weights as described for 2/3 testing (see left column) while the BAC mice, which develop excess fat deposits, were restricted gradually to the point where their food consumption matched that of the 85% WT animals in a 30 min free feeding test, at which point they were slightly heavier than controls. Exp. 1: n=7 genotype, 84 weeks of age at the start of testing; Exp. 2: n=23 genotype, 78 weeks of age at the start of testing; Exp. 1: n=11 genotype, 48 weeks of age at the start of testing. Exp. A: n=13 genotype, 26 weeks of age at the start of testing.

Due to the advanced age of the mice at the time of testing, several animals died during the course of the experiment.

Apparatus: 8 adopted operant chambers, each with a food magazine and pellet dispenser and fitted with two touchscreen monitors on either side of the wall opposite the food magazine, were used in these studies. Software used to control stimulus delivery and data capture was provided by the Buxxy/Insite lab (Cambridge, UK).

Procedure: Pretraining: Mice were magazine trained and then trained on a simple CR/F/T 15 sec schedule, with pellets delivered following either a 15 sec presentation of a random stimulus or immediately following a nosepoke response to the stimulus. Subsequently, the contingency was modified such that reinforcement was only delivered on nosepoking and continued until mice reliably responded to presented stimulus; no genotype effects were observed in this pretraining (data not shown).

Discrimination training: Subjects were reinforced with a food pellet for a nosepoke response to one of two presented stimuli (stimulus pair 1) presented on a pseudo-randomly chosen side. Incorrect responses were followed by a 5 sec timeout period (house light off, no stimuli presented) and were followed by correction trials until the mouse responded correctly; data from these correction trials were not included in the percent correct choices presented here.

Reversal training: Once the animals reliably learnt the initial discrimination task (70% correct on at least 2 days), a contingency reversal was implemented, such that the previously non-reinforced stimulus became the reinforced stimulus and vice versa.

Novel Stimuli: Following acquisition of this reversal (70% correct on at least 2 days), an intradimensional shift phase, was implemented with two new stimuli (stimulus pair 2) trained just as in the initial discrimination phase.

Statistical analysis conducted with SAS and StatView software (SAS Institute), alpha level of 0.05 adopted throughout.

Results

Experiment 1: BAC mice Cohort 1

Discrimination. Acquisition of the visual discrimination did not significantly differ in WT vs. BAC HD mice (see Figure 2, left). Five BAC HD and two WT mice did not reach the 70% correct choice criterion during this training phase and were thus excluded from subsequent phases of testing.

Reversal. BAC HD mice performed significantly less well than did WT controls during reversal learning, particularly during the later part of this phase (Genotype main effect: F(1,36)= 6.43, p<0.05; Genotype x Session interaction: F(19,684)=2.13, p<0.01; see Figure 3, middle).

Novel Stimuli. Similarly, the BAC HD mice performed less well than WT mice during the later part of the Novel Stimuli phase (Genotype main effect: N5; Genotype x Session interaction: F(26,858)=1.98, p<0.01).

Figure 3: Percent correct choices of WT and MT mice during the A) Discrimination, B) Reversal and C) Novel Stimuli phases in Experiment 1. Data are expressed as mean ± SEM.

Experiment 2: BAC mice Cohort 2

Figure 4: Percent correct choices (mean ± SEM) of WT and z_Q175 KI HET mice during the Discrimination, Reversal and Novel Stimuli phases in Experiment 2. The dotted line indicates chance level (50%).

Experiment 3: Z_Q175 at 48 weeks

Discrimination. There were no differences between MT Q175 mice and WT controls in the acquisition of the visual discrimination task [Genotype: F(1,22)=0.78, n.s.; Genotype X Days: F(28,695)=0.80, n.s.], both groups exhibited a significant increase in accuracy across days [F(28,695)=8.12, p<0.001; Figure 3]. Four WT and four MT mice were excluded from the reversal phase due to a failure to reach at least 70% correct for 2 consecutive test sessions.

Reversal: Z_Q175 HET subjects exhibited a progressively greater deficit in accuracy compared to the WT control subjects as testing progressed [Genotype X Days: F(24,399)=3.18, p<0.001; Genotype: F(1,14)=7.37, p<0.05; Days: F(24,399)=27.91, p<0.001; Figure 3].

Novel Stimuli: Two MT mice were lost due to ill health prior to completion of the novel stimuli phase: their data were excluded from analyses. All mice, irrespective of genotype [Genotype X Days: F(24,349)=1.14, n.s.; Genotype: F(1,12)=0.80, n.s.], showed an improvement in discrimination during the novel stimuli phase [Days: F(24,349)=7.98, p<0.001; Figure 3].

Figure 5: Percent correct choices (mean ± SEM) of WT and Z_Q175 mice at 26 weeks during the Discrimination, Reversal and Novel Stimuli phases in Experiment 4. The dotted line indicates chance level (50%).

Discrimination: Although there were no differences between MT Q175 mice and WT controls in the initial stages of acquisition of the visual discrimination task, a deficit in the MT Q175 subjects emerged around Day 18 [Genotype X Days: F(28,666)=2.50, p<0.001; Days: F(28,666)=17.83, p<0.001; Genotype: F(1, 21)=0.78, n.s.; Figure 4]. Three MT, but no WT, mice were excluded from the reversal phase due to a failure to reach at least 70% correct for 2 consecutive test sessions in the Discrimination phase.

Reversal: Q175 HET subjects exhibited a progressively greater deficit in accuracy compared to the WT control subjects as testing progressed [Genotype X Days: F(24,499)=3.20, p<0.001; Genotype: F(1,18)=14.46, p<0.001; Days: F(24,499)=57.13, p<0.001; Figure 4].

Novel Stimuli: The Q175 mice exhibited a deficit only at the end of the novel stimuli phase [Genotype X Days: F(24,499)=3.37, p<0.001; Genotype: F(1,18)=0.84, n.s.; Days: F(24,499)=12.23, p<0.001; Figure 4].

Conclusions

Our results suggest that the BAC and z_Q175 HD models present cognitive deficits consistent with the cognitive inflexibility and psychomotor impairments described in HD patients. We propose that this touchscreen assay may be a useful test for exploring the effects of potential therapeutic manipulations on impaired cognitive function in this and other murine models of HD.

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