Deficient Object Location/Paired Associates Learning in the Q175 KI Mouse Model of Huntington's Disease

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1 BACKGROUND

Huntington's disease (HD) is a fatal neurodegenerative disorder characterized by uncontrolled movements, psychiatric disturbances and cognitive impairment that likely arise as a consequence of selective loss of striatal medium spiny neurons and forebrain atrophy. At present, only symptomatic treatments for psychiatric symptoms and chorea manifestations are available, whereas there is an utmost need in drugs able to modify HD time course.

HD is caused by expansion of polyglutamine (polyQ)-encoding tract in exon 1 of the huntingtin (*HTT*) gene to greater than 35 CAG repeats. Modeling HD in mice typically requires knock-in mutations causing expression of CAG tracts in mouse *Htt* gene that are longer than those in individuals with HD. Moreover, only a few preclinical mouse HD models are able to replicate HD phenotypes when the underlying mutation is heterozygous, i.e., genetically similar to human condition. One such model is Q175 (Menalled *et al*., 2012), in which motor and cognitive disturbances have been observed in heterozygous mutants.

Assessment of cognitive performance in mouse models of neurodegenerative diseases, including HD models, often relies on approaches that are not easily translatable to the clinical setting. One technique that has been increasingly applied for translational analysis of cognition in rodents uses touch-sensitive screens. In such tests, the stimulus (images in different locations on the screen) and reaction (touch) are similar to those employed in human cognitive assessments, such as the Cambridge Neuropsychological Test Automated Battery (CANTAB). Touchscreen tests have revealed subtle cognitive phenotypes in multiple models of brain disorders (Horner *et al*., 2013). To this end, we sought to examine performance of Q175 mice in the touchscreen version of Object Location/Paired Associates Learning (PAL) task (Horner *et al*., 2013), because individuals diagnosed with HD exhibited deficits in the human versions of the PAL task (Lange *et al*., 1995; Begeti *et al*., 2016).

2 METHODS

In this study, we used 12 Q175 HET and 15 WT age-matched male mice. The animals were 11 months old at the start of the experiments. Mice were housed at a standard temperature (22 ± 1°C) and in a light-controlled environment (lights on from 7 am to 8 pm). During the experiment, mice were kept on a restricted diet at 85–90% of their free-feeding weight in order to maintain motivation for the task. Mice received one 60-min long training session per day in the afternoon hours, 5–7 days per week.

Prior to the Paired Associates Learning (PAL) test, the mice were trained on basic touchscreen task requirements, which were introduced gradually, as previously described (Horner et al., 2013).

During the 36-trial (or maximum 60-min long) daily PAL sessions, mice were presented with a pair of stimuli, one in each of two locations (left, middle or right; the third being blank and non-responsive). There were three possible stimuli ("Lines Grid-Right", "Lines Grid-Left" and Horizontal lines") with dark and light lines going in different directions (Fig. 1). On each trial, the correct (S+) stimulus was determined by a combination of stimulus shape (the "object") and its location, e.g., horizontal lines image was correct in the left location, Grid-Right image — in the middle, and Grid-left image — on the right. On each trial, one stimulus was presented in its correct location along with one of the two alternative stimuli in its incorrect location (S-), giving a total of six possible trial types. Stimuli remained on the screen until the S+ or S- was touched, and were removed immediately following a touch to either; touches to the blank inactive location were ignored. Response to the S+ was rewarded (tone, reward drop of milkshake delivered, magazine light on, no "time out"); response to the S- was "punished" (houselight on for a 5-s "time out", no milkshake delivery). Incorrect responses to S- were followed by a correction procedure.

3 RESULTS

Figure 1. Illustration of the PAL task in touchscreen chamber.

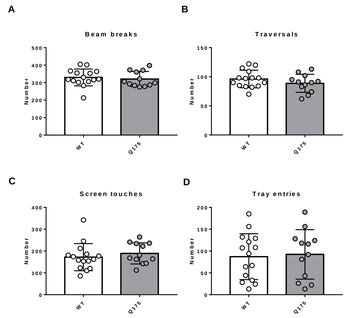

Figure 2. Normal locomotor activity of Q175 mice upon the first exposure to touchscreen chamber.

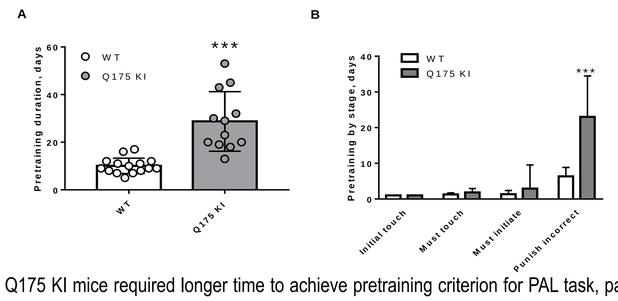

Figure 3. Q175 KI mice required longer time to achieve pretraining criterion for PAL task, particularly, during "Punish Incorrect" stage. Data are presented as the mean ± standard deviation. $N_{Q175\ KI}$ = 12; N_{WT} = 15.

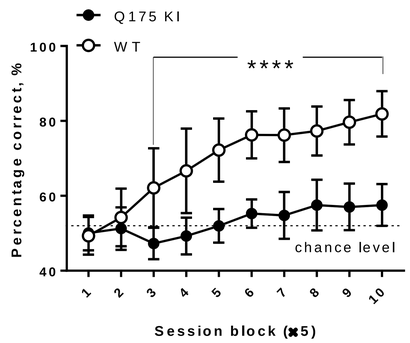

Figure 4. Q175 KI mice demonstrated profoundly impaired learning of the PAL task.

Data are presented as the mean ± tandard deviation.****P < 0.0001 (*post hoc* Holm-Sidak's multiple comparisons test). $N_{Q175\ KI}$ = 12; N_{WT} = 15.

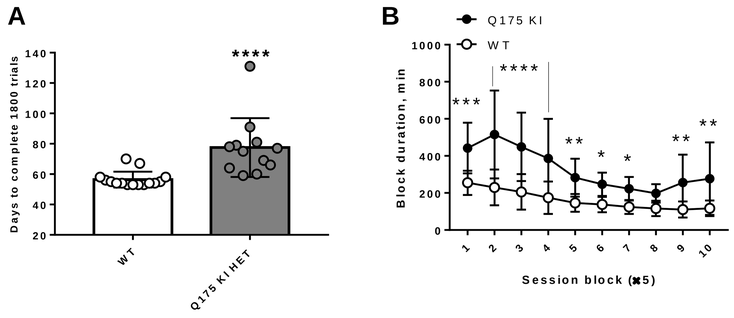

Figure 5. Q175 KI mice required longer time to complete required 1800 PAL sessions (A) and had longer daily session durations throughout the whole period of testing in the PAL tasK (B). Data are presented as the mean ± standard deviation. $N_{Q175\ KI}$ = 12; N_{WT} = 15.

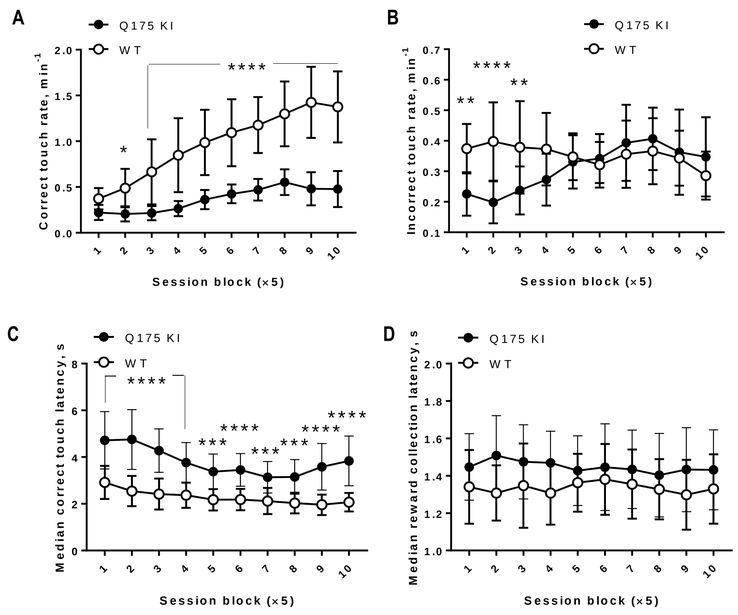

Figure 6. Slower and less selective performance of Q175 KI mice in the PAL task. Mutant animals exhibited consistently slower target touch rate (A) and slower incorrect touch rate only in the initial period of PAL testing (B). Note contrasting patterns of incorrect touch rate curves in the two groups. Q175 KI mice also demonstrated consistently longer latency to touch the target (C), whereas latencies to collect liquid food reward were similar (D). The latter circumstance suggests that mutant animals had no gross motor impairment and were motivated by the reward to the same extent as were WT mice. Data are presented as the mean ± standard deviation. $N_{Q175\ KI}$ = 12; N_{WT} = 15.

4 CONCLUSIONS

- Q175 KI mice demonstrated profoundly impaired performance in the Paired Associates Learning task as they remained below 60% correct response performance level at the last set of five PAL sessions. In contrast, WT mice exhibited a steady improvement in their performance, having achieved 80%-level of correct responses by the end of testing.
- Deficient learning of the PAL task by Q175 KI mice was associated with slower and less selective performance although the reaction to the reward was similar to that in WT mice.
- Impaired learning of the PAL touchscreen task in Q175 KI mice parallels deficient performance of individuals diagnosed with Huntington's disease in the human versions of the PAL task (Lange et al., 1995; Begeti et al., 2016).
- Lower responding rate of Q175 mice expressed in the lower number of trials made per day may be an indication of an apathic phenotype, i.e. lower motivation to work for reward. Because apathy is an important symptom in HD, assessment of Q175 KI mice in more specific tests of motivational behavior and reward-related decision making is warranted.

5 REFERENCES

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