

Hypothalamic expression of huntingtin causes distinct metabolic changes in the R6/2 and BACHD models of Huntington's disease

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Background

Underlying mechanisms of metabolic changes in Huntington's disease (HD) are not fully known, but studies suggest involvement of hypothalamic dysfunction (1, 2). A higher body mass index has been associated with slower disease progression (3), indicating that metabolic changes may be involved in disease pathogenesis.

Aim

To investigate whether increased levels of hypothalamic huntingtin (HTT) affects metabolic phenotype and disease features in R6/2 and BACHD mouse models that respectively develop lean- and obese phenotypes.

Viral vector-induced HTT expression in hypothalamus

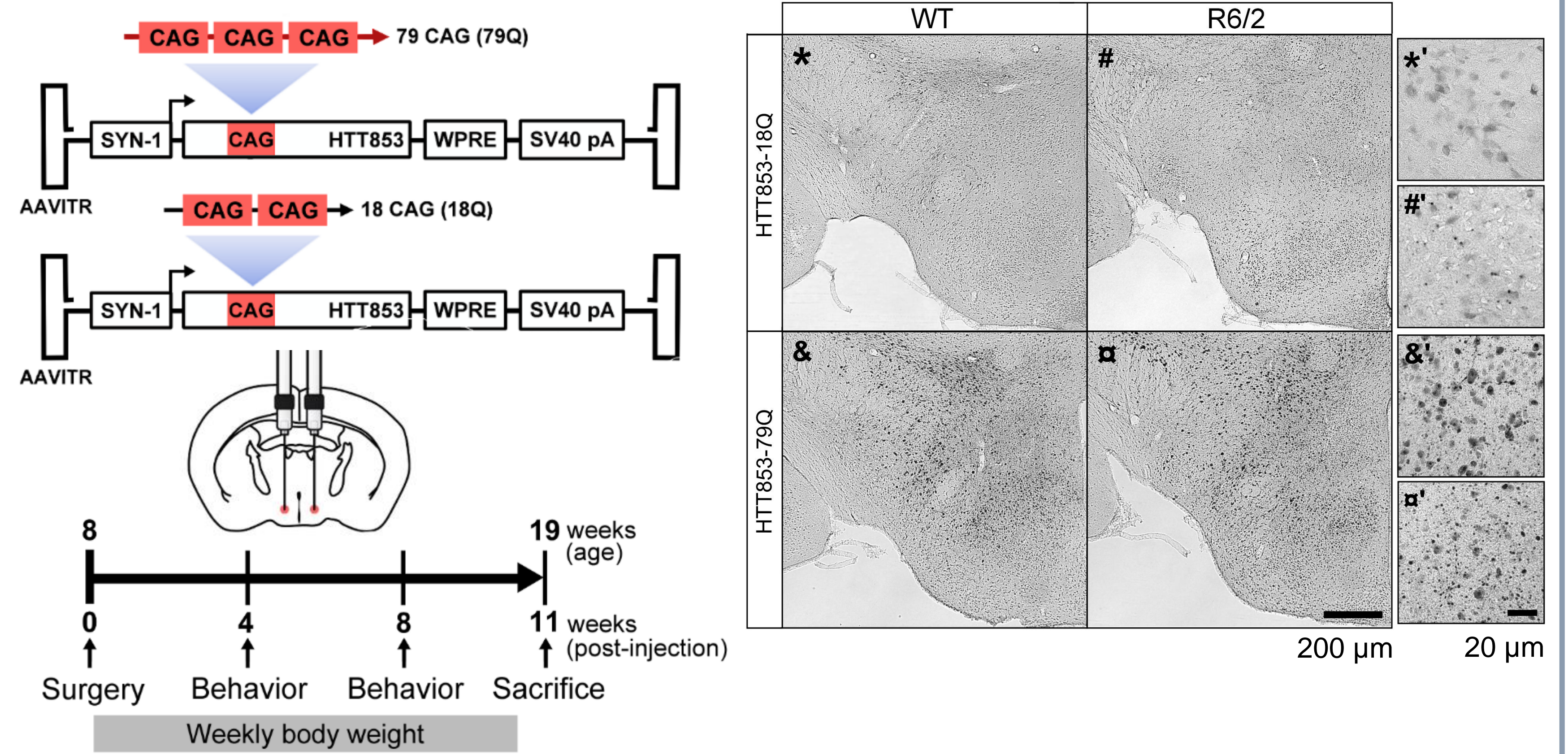


Figure 1. Adeno-associated viral vectors (rAAV2/5) expressing N-terminal fragments of human huntingtin (HTT) of 853 amino acids in length under control of the human Synapsin-1 (Syn-1) promoter. Wild-type (18 CAG; HTT853-18Q) and mutant (79 CAG; HTT853-79Q) HTT. The timeline shows experimental setup for studies in R6/2 mice of CAG 279-310. WT = wild-type.

Weight changes in BACHD and wild-type females

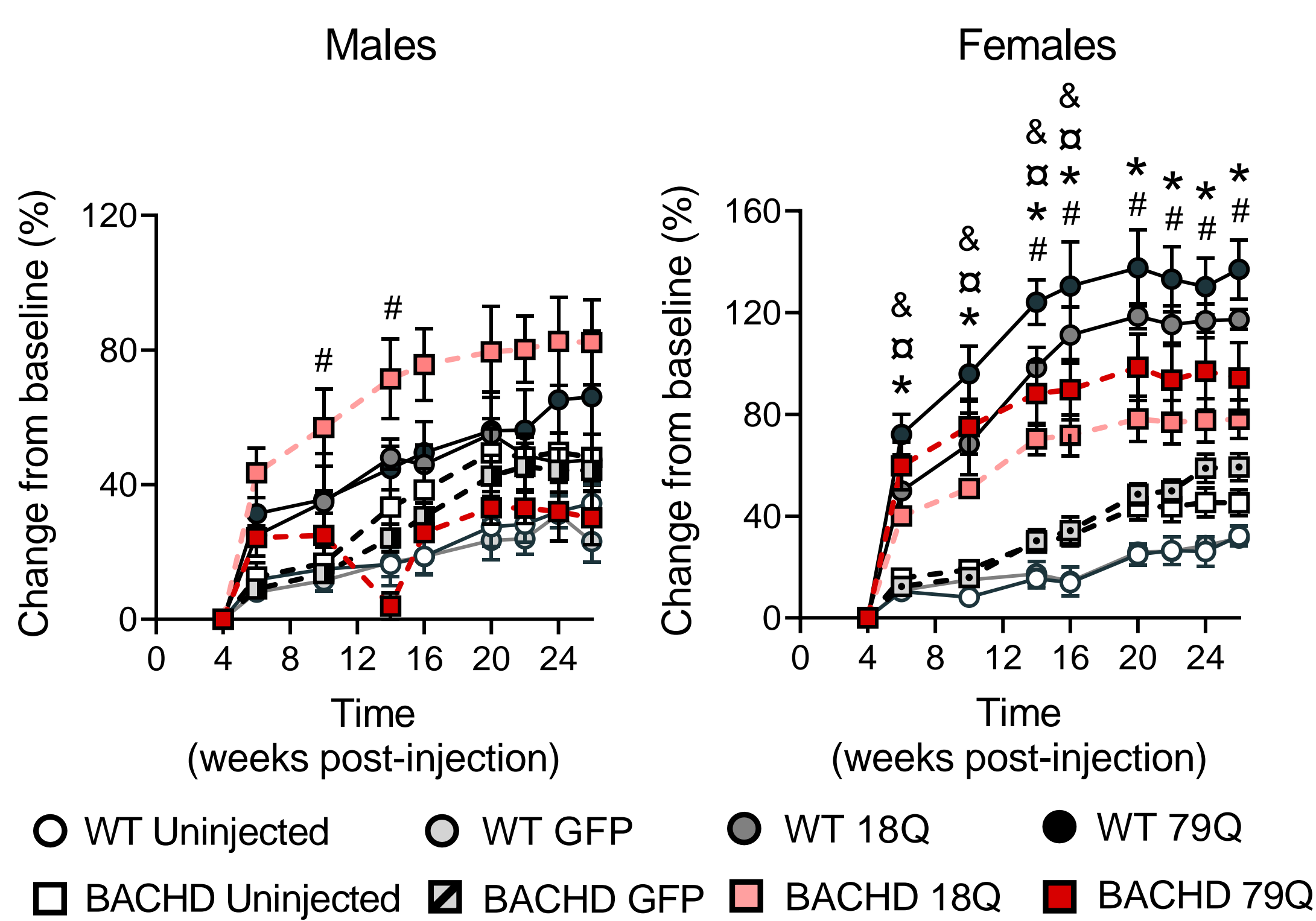


Figure 2. BACHD female mice (full-length 97 CAG HTT) and wild-type littermates with overexpression of 79Q HTT in hypothalamus displayed a percent change in endpoint body weight from baseline of 106 ± 15.23 and 77.37 ± 10.51 respectively. 18Q = HTT853-18Q vector and 79Q = HTT853-79Q vector. WT = wild-type. * $p < 0.05$ WT 79Q vs WT uninjected, # $p < 0.05$ WT 18Q vs WT uninjected, & $p < 0.05$ BACHD 79Q vs BACHD uninjected, $\& p < 0.05$ BACHD 18Q vs BACHD uninjected.

Body weight, body fat and behavioral alterations in R6/2 females

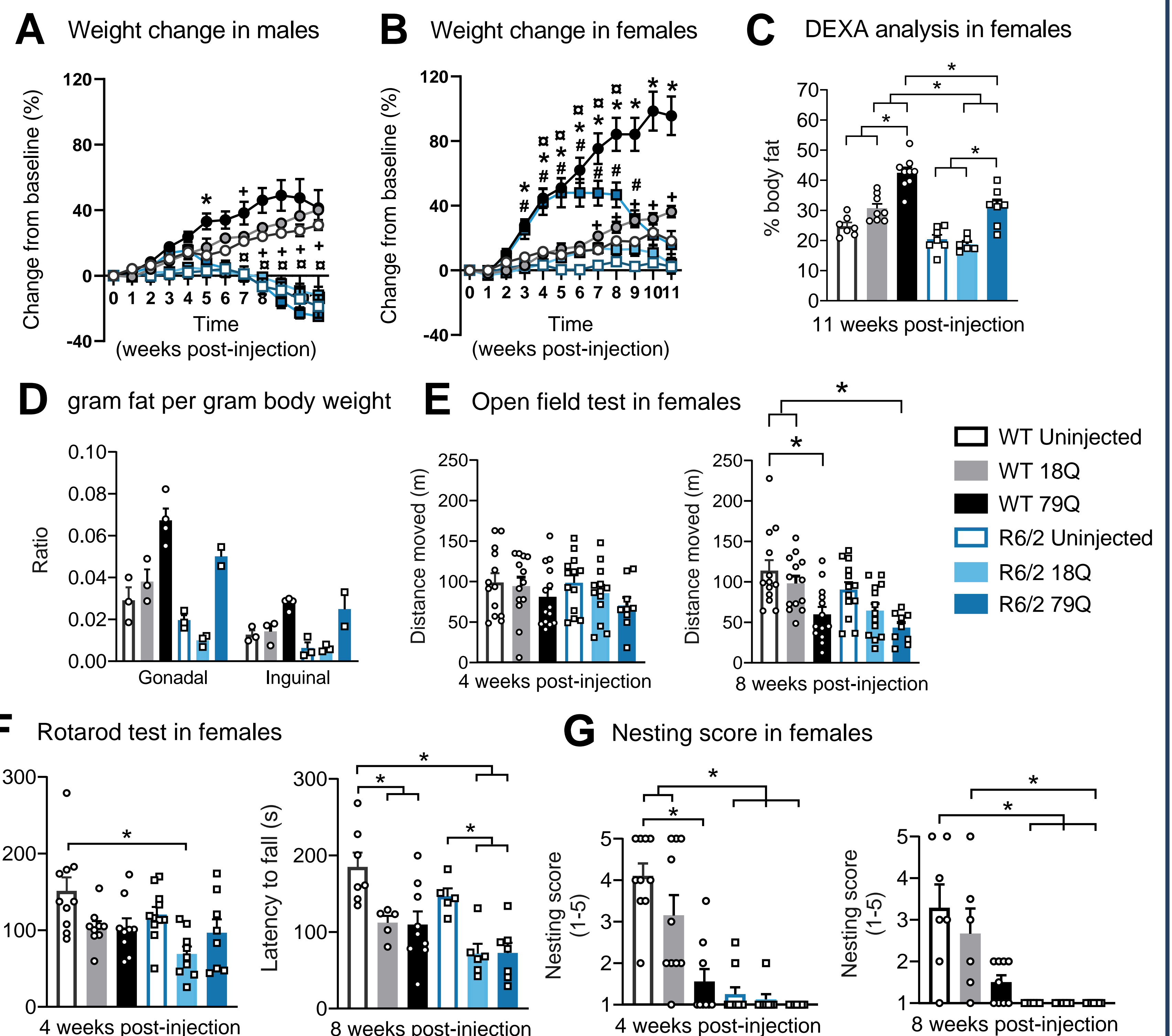


Figure 3. Percent weight change from baseline weight in R6/2 males (A) and females (B) with their respective wild-type littermates. * $p < 0.05$ WT 79Q vs WT uninjected, $\& p < 0.05$ R6/2 79Q vs WT uninjected, + $p < 0.05$ R6/2 uninjected vs WT uninjected, # $p < 0.05$ R6/2 79Q vs R6/2 uninjected. (C) Percentage body fat in females measured by DEXA analysis. (D) Weighed white fat depots at sacrifice in female mice, gonadal (visceral) and inguinal (subcutaneous). (E-G) Behavioral analyses in females performed at 4- and 8 weeks post injection. (E) Open field, (F) Rotarod and (G) Nesting test. 18Q = HTT853-18Q vector and 79Q = HTT853-79Q vector.

Altered food intake and metabolic rate in R6/2 females

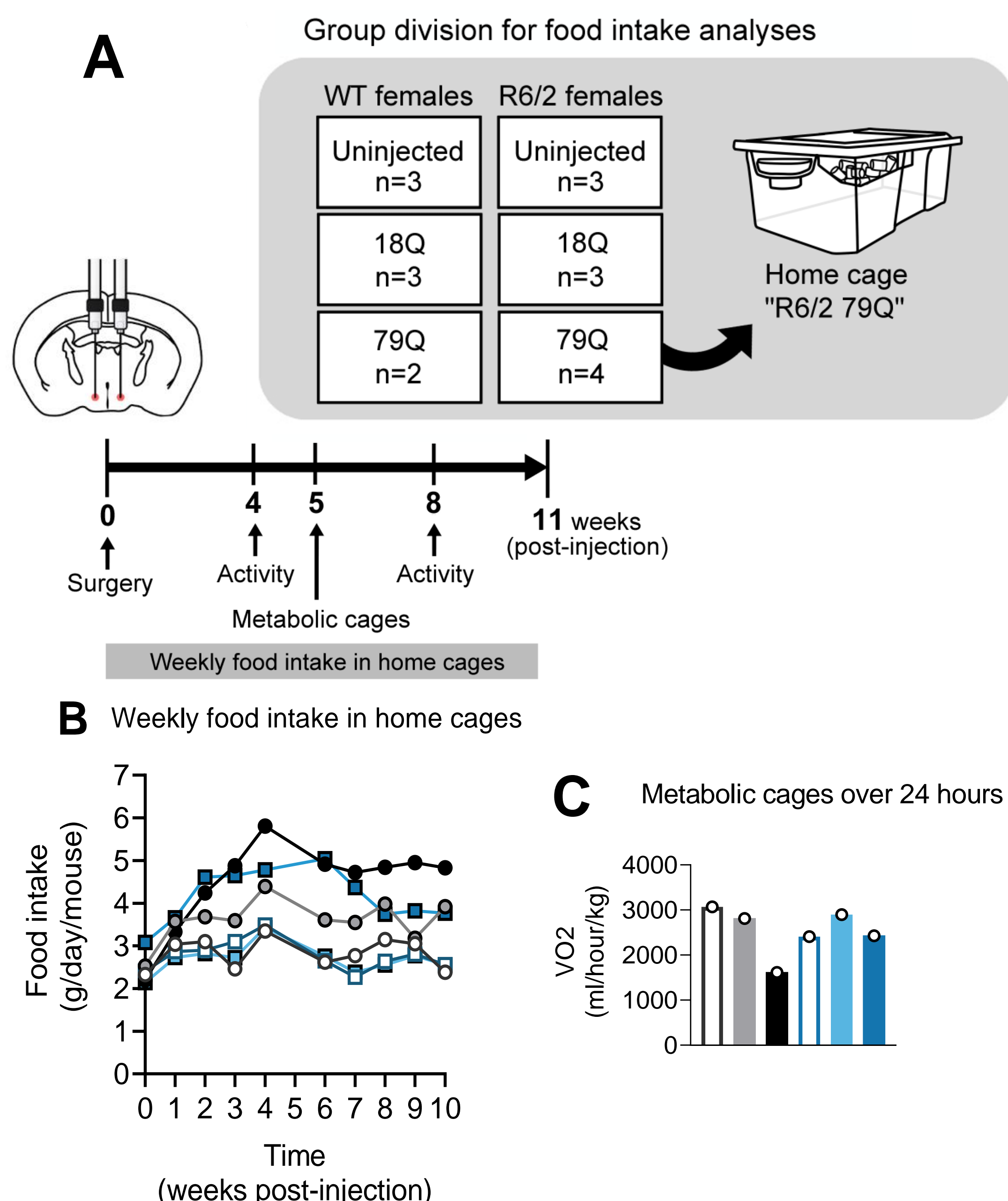


Figure 4. (A) For assessment of weekly food intake, females of the same genotype (wild-type or R6/2) and HTT vector (18Q, 79Q or uninjected) were divided into groups of $n=2-4$ in home cages. (B) Weekly food intake in home cages (gram/mouse/day) for each cage. (C) At 5 weeks post-injection, mice from each experimental group were analyzed in groups in metabolic cages.

Conclusions

- Overexpression of hypothalamic HTT affects weight in HD mice
- The response to hypothalamic overexpression of HTT is modified by gender
- Hypothalamic HTT cannot prevent late-stage weight loss in R6/2 mice

References

1. Hult, S., et al. Cell Metabolism, 2011.
2. Soyly-Kucharz, R., et al. Scientific reports, 2015.
3. van der Burg, J.M.M., et al. Annals of Neurology, 2017.