Targeted Circuit Manipulation for Ameliorating Huntington's Disease Pathogenesis

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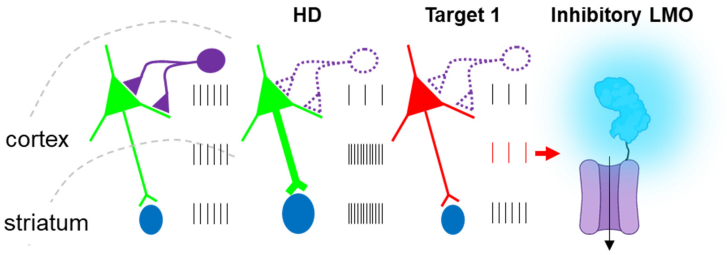
BACKGROUND

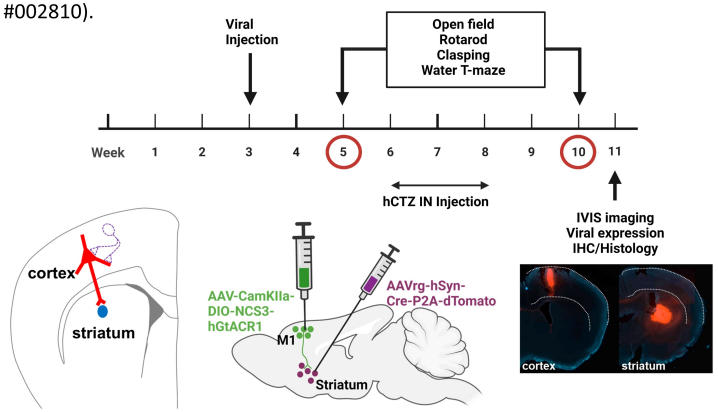
Huntington's disease (HD) is an autosomal dominant inherited neurodegenerative disorder in the brain, causing abnormal movements (chorea), and cognitive and behavioral impairments.

Based on findings in humans and animal models we know that there are circuit imbalances in HD, even before onset of symptoms.

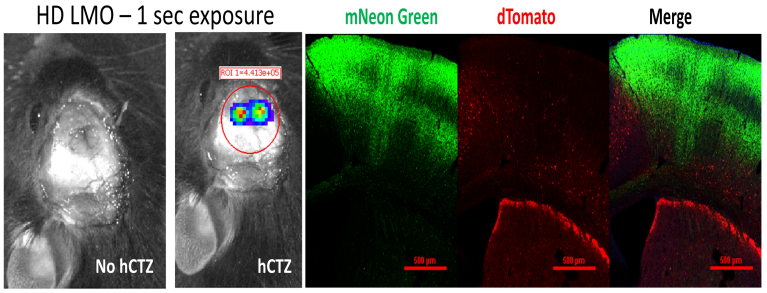


EXPERIMENTAL DESIGN

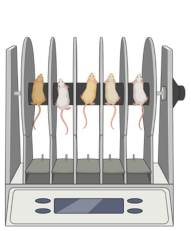
Wild-type (WT) female B6CBA mice transplanted with R6/2 ovaries (CAG 160 +/- 5) and WT male littermates were obtained from The Jackson Laboratory (stock #002810).

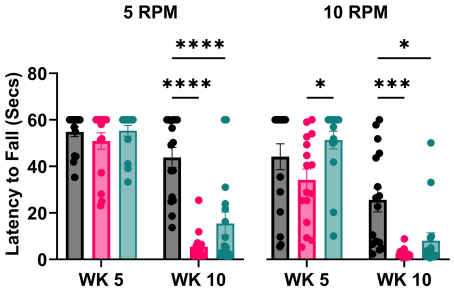


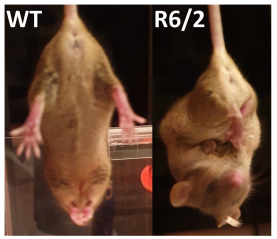
Robust bioluminescence and fluorescence in R6/2 mice injected with AAV expressing the inhibitory luminopsin



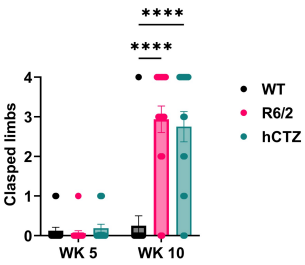
A. Loss of motor coordination and clasping response in R6/2 mice are not alleviated with treatment


Rotarod

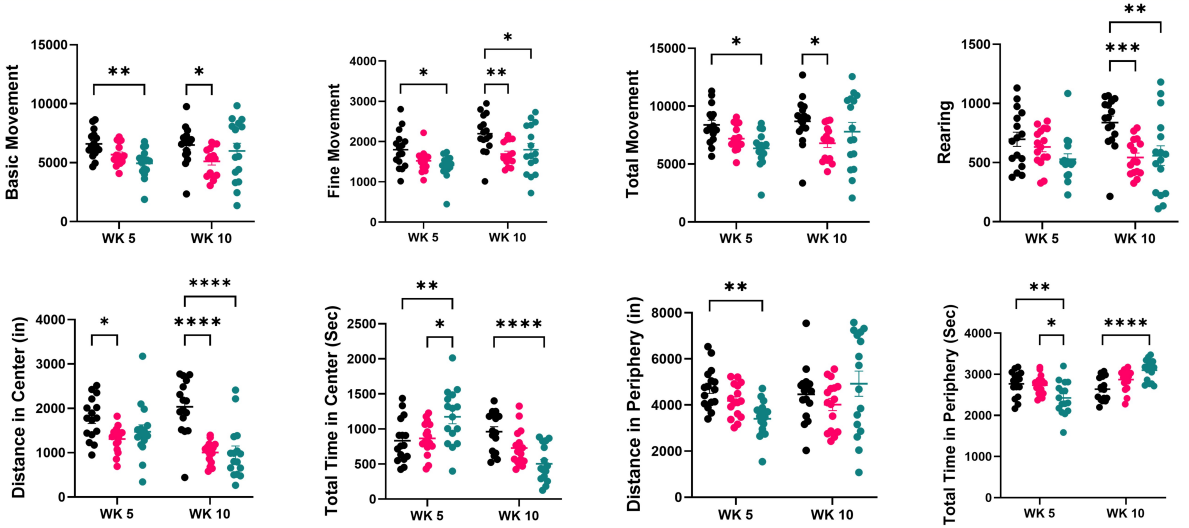




Clasping

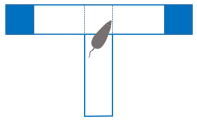


B. Inhibition of the cortical-striatal neurons did not attenuate dysfunctional exploratory and anxiety-like behaviors in R6/2 mice

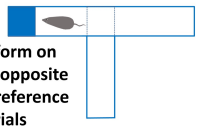


C. Water T-maze test revealed motor deficits in R6/2 mice

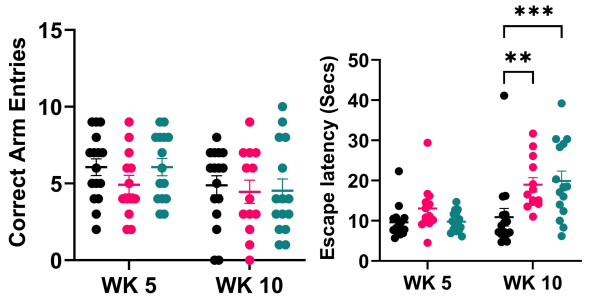
Day 1: Identify side preference



Day 2: Number of correct arm entries & Escape latency



- Platform on side opposite to preference
- 10 trials



CONCLUSION & FUTURE DIRECTIONS

- Presymptomatic dampening of cortical-striatal projection neuron activity does not alleviate HD symptoms.
- Perform experiments with Emx1-Cre/DIO-iLMO.
- Start experiments on enhancing activity of PV interneurons.

ACKNOWLEDGMENTS

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