Striatal Dopamine Dynamics and Motor Learning in a Mouse Model of Huntington Disease

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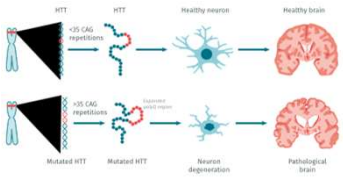
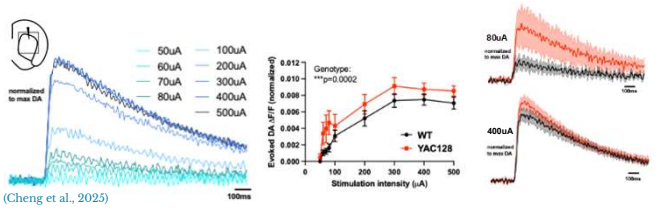
Background

- **Huntington Disease (HD)** is an inherited neurodegenerative disorder that often leads to **impaired motor learning and execution**, likely influenced by **altered dopamine (DA) signaling in the striatum**



- However, currently there are no studies that directly measure DA during motor tasks in early HD
- We previously found **increased evoked DA** in striatal slices in the premanifest YAC128 transgenic HD mouse model (Cheng et al., 2025)

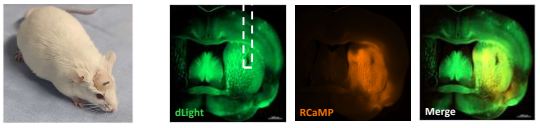


(Cheng et al., 2025)

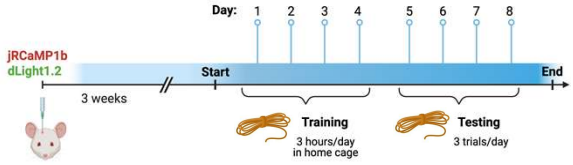
- In this study, we aim to compare behavioural and neural patterns between YAC128 and wild-type (WT) mice during motor learning by **simultaneously measuring striatal calcium transients (as a proxy for neuronal activity) and DA release using optogenetic sensors**

Methods

- 2-3-month-old YAC128 mice and WT littermates received RCaMP (red calcium sensor) and dLight (green DA sensor) AAV injections in the right dorsal striatum for real-time imaging with fiber photometry

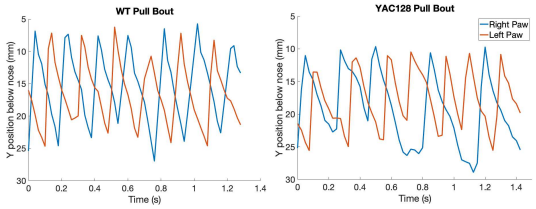


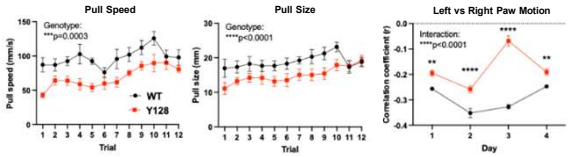
- Mice were trained prior to testing by placing 1m-long strings baited with Froot Loops in their home cage for 3 hours/day for 4 days
- String-pulling behavior was video recorded and tracked using DeepLabCut pose estimation software
- String-pulling motions were analyzed and correlated to photometry signals



Results

String-Pulling: Behaviour Analysis

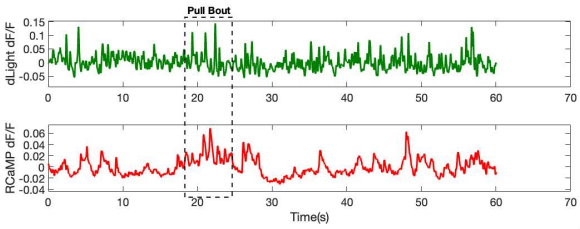


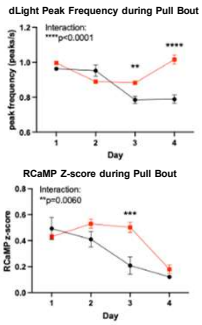


- YAC128 mice make slower and smaller motions on the string-pulling task
- Anti-correlation between left and right paws is weaker in YAC128 than WT

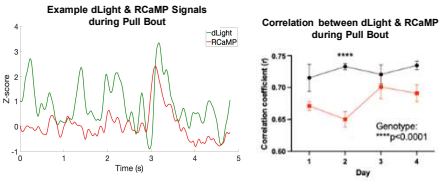
Example string-pulling video:

String-Pulling: Photometry Analysis





- YAC128 mice show hyperactive striatal calcium activity and dopamine peak frequency during string-pulling compared to WT



- WT mice show a stronger correlation between striatal calcium and dopamine transients during string-pull bouts compared to YAC128

Conclusion

- Premanifest YAC128 mice show **altered movement kinematics and striatal DA patterns** when engaged in specific motor behaviours
- **We are the first to combine real-time imaging of striatal DA with behaviour in an HD rodent model**, and identifying altered DA signaling patterns that occur during both the execution of specific motor movements and more broadly in the regulation of motor learning are crucial for guiding therapeutic efforts in correcting uncontrolled movements in HD

References

- Cheng, J., Koch, E. T., Ramandi, D., Mackay, J. P., O'Leary, T. P., Rees-Jones, W., & Raymond, L. A. (2025). Synaptic modulation of glutamate in striatum of the YAC128 mouse model of Huntington disease. Neurobiology of Disease, 205, 106774.

Acknowledgements

Djavad Mowafaghian CENTRE FOR BRAIN HEALTH
NUNC
CIHR IRSC Canadian Institutes of Health Research / Instituts de recherche en santé du Canada
UBC Neuroscience
UBC Department of Psychiatry
NSERC CRSNG