ALTERED STRIATAL ACTIVITY AND MOTOR KINEMATICS IN A MOUSE MODEL OF HUNTINGTON DISEASE

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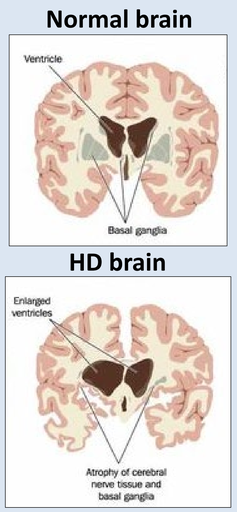
1. BACKGROUND

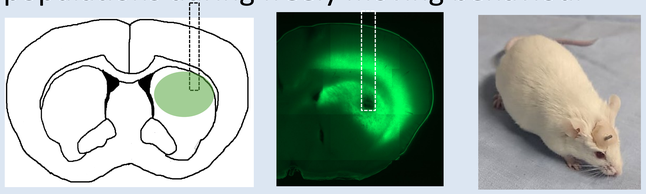
- Huntington's disease (HD) is a progressive, deadly neurodegenerative disease that leads to motor, cognitive, and psychiatric symptoms



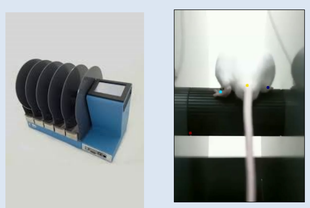
- HD mouse models have been created using the mutant *HTT* gene, to model disease symptoms and neuropathology
- In vitro studies have shown changes to neurotransmission and synaptic plasticity in HD mice, but how this relates to behavioural symptoms in vivo is still unclear
- **We aim to determine how neural activity is altered in the YAC128 HD mouse model during motor learning and spontaneous behaviour**

2. METHODS

- Fiber photometry is a method to image neuron populations during freely moving behaviour



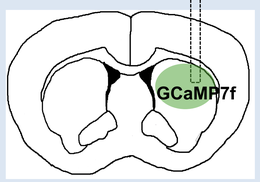
- **We are measuring striatal activity using fluorescent calcium sensors during motor learning on the accelerating rotarod in the YAC128 HD mouse model**



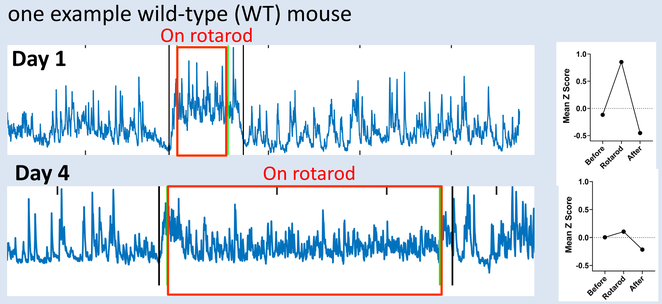
3. RESULTS

Overall striatal activity decreases over the course of rotarod training in wild-type mice

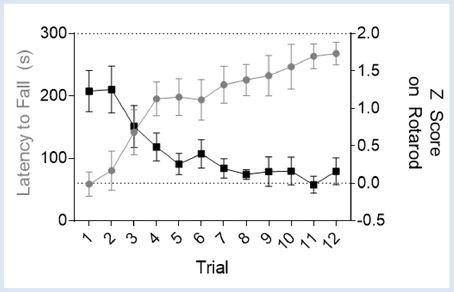
- GCaMP7f expressed non-specifically under a synapsin promoter in all striatal neurons



- Striatal neural activity during rotarod performance (red box) during early training (Day 1) and late training (Day 4) from one example wild-type (WT) mouse

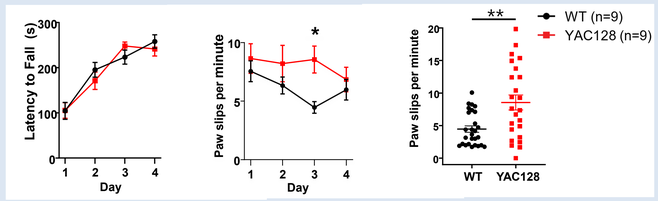


- As mice learn the rotarod task, latency to fall improves, and average striatal GCaMP7f activity (Z Score) decreases

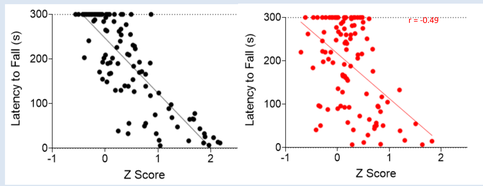


Pre-manifest YAC128 HD mice show changes to striatal activity and paw kinematics on rotarod

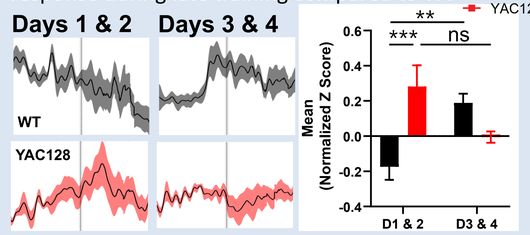
- 2-3 month old ('pre-manifest') YAC128 mice did not show deficits in latency to fall, but did show changes to paw kinematics including an increased number of paw slips below the bottom of the rotarod



- WT mice showed a strong correlation between latency to fall and GCaMP7f activity in striatum. This correlation is significantly weaker in YAC128 mice.

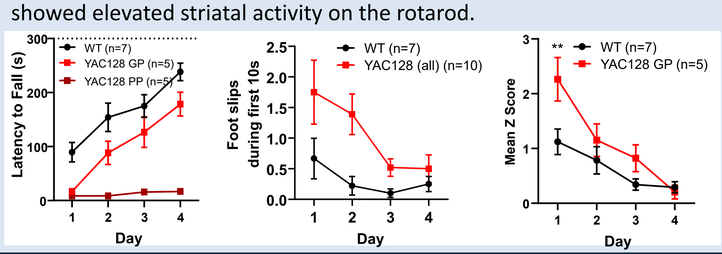


- YAC128 mice showed elevated striatal activity following paw slips during early training, and a greatly reduced response during late training compared to WT



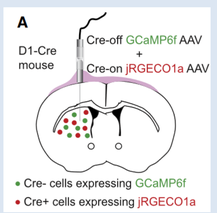
Manifest YAC128 mice show severe rotarod deficits and elevated striatal activity

- 6-7 month old ('manifest') YAC128 mice displayed deficits in latency to fall and many paw kinematic measures. We divided YAC128 mice into those that could learn the task (GP) and those that could not (PP). YAC128 GP mice showed elevated striatal activity on the rotarod.

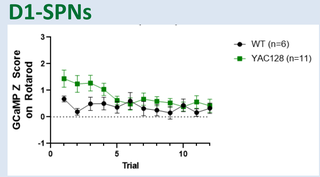


Activity is elevated in both D1- and D2-SPNs in manifest YAC128 mice

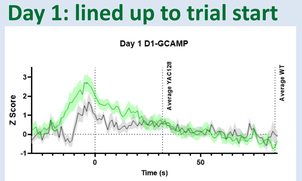
- >90% of neurons in the striatum are spiny projection neurons (SPNs) of two main types: D1-SPNs (involved in promoting movement) and D2-SPNs (involved in suppressing unwanted movements).
- We expressed green (GCaMP6s) and red (RCaMP1b) calcium sensors in **D1-SPNs** and **D2-SPNs** respectively to look at simultaneous activity in these populations during rotarod learning
- We found that activity of D1-SPNs was higher in manifest YAC128 initially and then returned to WT levels by late training, whereas activity D2-SPNs was elevated throughout training in manifest YAC128



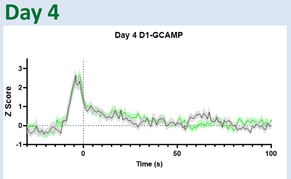
D1-SPNs



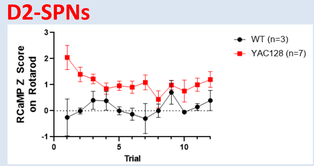
Day 1: lined up to trial start



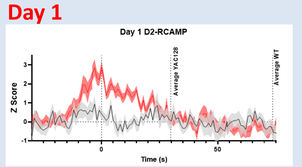
Day 4



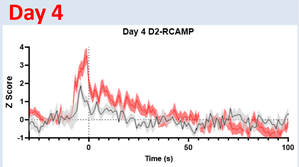
D2-SPNs



Day 1



Day 4



4. KEY FINDINGS

- YAC128 mice show paw kinematic deficits on rotarod starting at a young age, and altered striatal activity during rotarod performance
- Pre-manifest YAC128 mice exhibit a weaker correlation between rotarod performance and striatal activity, and altered striatal activity surrounding paw slips
- Manifest YAC128 mice display increased overall striatal activity, and increased population activity of D1- and D2-SPNs