Novel Measures of Apathy in Huntington's Disease: Cross-Sectional and Longitudinal Analysis

Emily Hare [1], Dr Duncan McLauchlan [2] and Professor Anne Rosser [2]

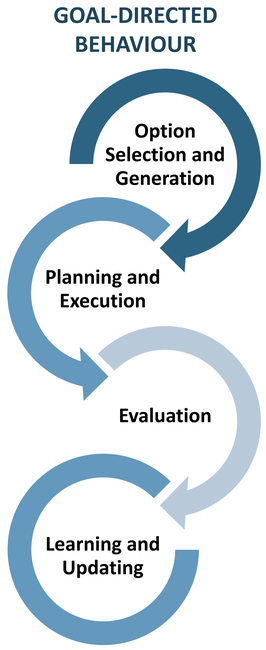
[1] School of Medicine, Cardiff University
[2] Division of Psychological Medicine and Clinical Neurosciences

BACKGROUND

- Apathy is a core symptom of HD, presenting up to 10 years before the onset of motor symptoms and worsening alongside disease progression.[1,2]
- It is hugely detrimental to the quality of life (QoL) of people with HD, both functionally and socially.[3]
- Apathy is best defined as a deficit in goal directed behaviour,[4] involving several stages.
- Apathy has potential as a indicator of disease progression given that its severity tracks disease progression and it is highly prevalent in the HD population.[5]
- The current gold-standard measurement of apathy in HD, is the Problem Behaviour Assessment (PBA) with a dedicated apathy section. It is a self-report measure and is vulnerable to variability, misinterpretation and bias.[6]
- In 2018, McLauchlan created a number of objective novel computer tasks designed to measure different aspects of goal directed behaviour: the Persistence task and the Maze task. These tasks were shown to be associated with PBA-apathy scores in an HD population.[7]
- There is a significant requirement for sensitive measures of disease progression that can be utilised in clinical research. Currently the most sensitive measure of change in HD is the composite UHDRS (cUHDRS), devised by Schobel et al.[8]
- The CAPIT-HD2 study (CAPIT-HD; Core Assessment Program for Intracerebral Transplantation in HD),[9] undertaken by the REPAIR-HD consortium, is aimed at developing novel measures that can sensitively track clinical change in HD, for the use in surgical trials with small cohorts.

AIM

Evaluating the longitudinal validity and sensitivity of the Persistence and Maze tasks to assess their potential utility in future clinical trials.



METHODS

- CAPIT-HD2 was run by the REPAIR-HD consortium made up of 4 centres: Cardiff, Manchester, Paris and Münster.
- Participants were recruited from the Enroll-HD cohort, including cases (83) and controls (54).
- Inclusion criteria: aged 18 or over; CAG repeat length of 36 or longer; stage I or II of the disease according to Total Functional Capacity (TFC) staging.
- Participants underwent a testing with a battery of established and novel tools measurements at baseline and 12 months later.
- This study compares the performance of the two novel tasks against multiple standardised tests – PBA-apathy, the UHDRS and the composite UHDRS score (cUHDRS).

Statistical Analysis

- Generalised linear models (GLM) were also used to test the association between the novel tasks and PBA-apathy at baseline and follow up.
- Receiver operating characteristic analyses (ROC) were performed to assess the task's ability to predict PBA-apathy.
- GLMs were used to assess the sensitivity of the standard clinical measures, as well as the novel tasks, over time; this analysis was performed on case data only.

PBA - APATHY

- Semi-structured interview to measure self-reported apathy symptoms
- Current gold-standard measure of apathy in HD

cUHDRS

$$= \left[\left(\frac{TFC - 10.4}{1.9}\right) - \left(\frac{TMS - 29.7}{14.9}\right) + \left(\frac{SDMT - 28.4}{11.3}\right) + \left(\frac{SWR - 66.1}{20.1}\right)\right] + 10$$

- Equation using elements of the UHDRS
- Current gold-standard for measuring disease progression

PERSISTENCE TASK

- Designed to measure sensitivity to aversion stimuli
- Required participants to take part in a car race on a computer, in which they were always losing
- Outcome measure: time taken to quit the race

MAZE TASK

- Designed to measure idea generation and option selection
- Participants presented with a series of 15 different scenarios and asked to decide what to do next
- Outcome measure: time taken to start giving answer

RESULTS

PARTICIPANT DEMOGRAPHICS

- There was no significant difference between the average age of cases (52.4) and controls (53.2).
- There was no significant difference in the male to female ratio between the groups or the years of education.
- Those with HD had an average CAG repeat length of 43 (range 38-62).

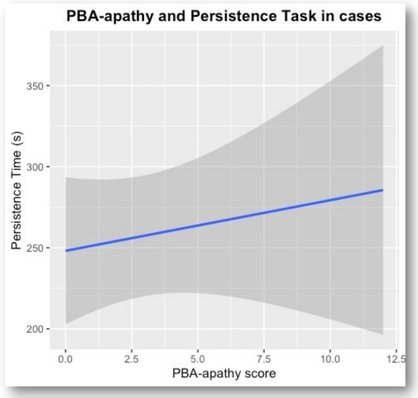
ASSOCIATION OF TASKS WITH PBA-APATHY

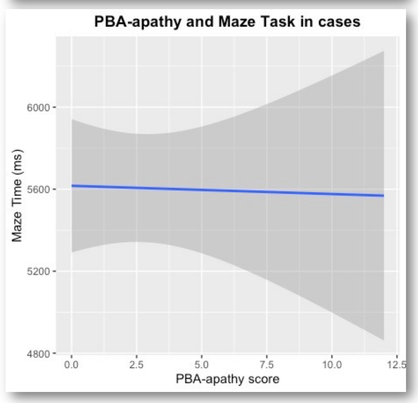
- ROC analysis suggested that the Persistence task (AUC=0.76) was a better predictor of apathy than the Maze task (AUC=0.71).
- This was supported by GLM analyses which found that Persistence task was associated with PBA-apathy at baseline (p=0.0162) whilst the Maze task was not (p=0.992).
- Neither task showed association with PBA-apathy score at follow up.

SENSITIVITY TO LONGITUDINAL CHANGE

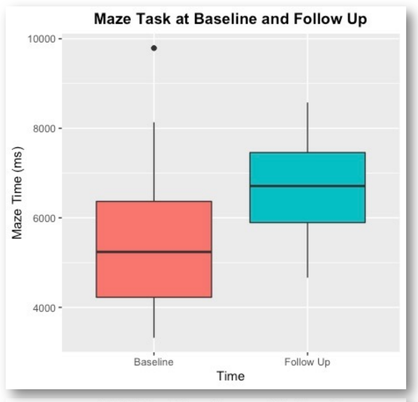
- Of all of the measures taken, the Maze task was found to be the only one that changed significantly from baseline to follow up (p=0.0044).
- The cUHDRS did not measure a significant change from baseline to follow up.

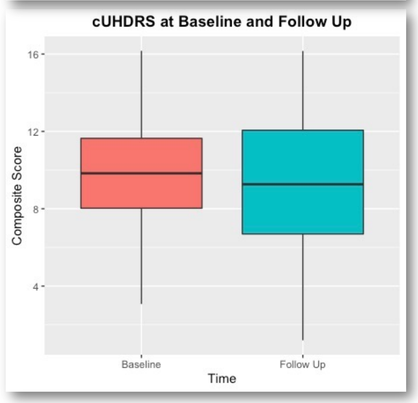
ASSOCIATION WITH PBA-APATHY





SENSITIVITY TO CHANGE LONGITUDINALLY





DISCUSSION

Summary

- Contrary to McLauchlan's findings[7] only the Persistence task was associated with apathy at baseline and this association was lost at follow up; this suggests that the tools are not reliable longitudinal measures of apathy in HD.
- However, the Maze task was found to be the only measure sensitive to change over the 12 months, superior to the current gold-standard, the cUHDRS.
- Currently, the lack of objective and sensitive measures of efficacy is a significant barrier to the development of therapeutics for HD, and other neurodegenerative disorders. Research is now needed to replicate the longitudinal performance of the Maze task in different HD populations, at varying stages of disease.

Discussion

- There may still be utility in the Persistence task cross-sectionally as an objective measure of apathy, especially given the current reliance on subjective measures.
- Recent work by Nair et al[10] found that insensitivity to negative stimuli is evident in the striatal response of gene positive individuals 25 years before the onset of motor symptoms.
- The Maze task relies upon idea generation and therefore to an extent may be measuring creativity. Creativity is heavily modulated by dopaminergic systems in the frontal-striatal brain circuits – an area of the brain heavily implicated in HD.

Limitations

- PBA-apathy, despite being the current gold-standard measure, has questionable validity and therefore may be a poor tool for comparison.
- The study spanned 4 different centres and therefore the tasks were performed in different languages and by different teams of researchers.

1. Duff K et al (2007) *Biological psychiatry* 62(12):1341-1346. 2. McColgan P et al. (2018) *European Journal of Neurology* 25(1):24-34. 3. Ready RE et al. (2008) *Journal of Movement Disorders* 23(5):721-6. 4.Levy R et al. (2006) *Journal of Neurology* 253 Suppl 7:Vii54-61. 5. Camacho M et al. (2018) *Journal of Alzheimer's Disease and Parkinsonism* 8(2). 6. Thompson JC et al. (2012) *The Journal of Neuropsychiatry and Clinical Neurosciences* 24(1):53-60. 7. McLauchlan DJ et al. (2019) *Journal of Movement Disorders* 34(9), pp. 1381-1391. 8. Schobel SA et al. (2017). *Neurology* 89(24), pp. 2495-2502. 9. Quinn N et al. (1996) *Movement Disorders* 11(2):143-150. 10. Nair A et al. (2021) *Biological Psychiatry* 10. Boot et al. (2017) *Neuroscience and Biobehavioural Reviews* 78:13-23.

Diagrams created with Biorender.com, Statistical software R used for data analysis and graph generation