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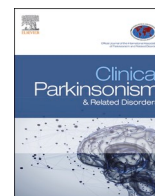
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## Short Communications

## Cognitive processes of apathy in Huntington's disease show high sensitivity to disease progression



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## ABSTRACT

**Background:** Disease-modifying treatments for Huntington's disease (HD) are entering clinical trials: there is a pressing need for objective outcome measures of disease progression. Our previous work showed an association between 2 novel, objective cognitive tasks and apathy - a core feature of disease progression in HD.

**Objective:** Evaluate the longitudinal validity and sensitivity of the novel Persistence and Maze tasks to assess their utility as clinical outcome measures in HD.

**Methods:** 83 participants positive for the HD gene and 54 controls performed a battery of established and novel tools, at baseline and 12 month follow up.

**Results:** The Maze task was found to be the most sensitive measure of change at 12 months, including the current gold-standard measure (the composite disease progression score).

**Conclusion:** The Maze task has potential as a novel outcome measure of disease progression in HD and may have utility in other major neurodegenerative diseases.

## 1. Introduction

Huntington's Disease (HD) is an autosomal-dominant neurodegenerative disorder focused on cortico-striatal networks and characterised by motor, cognitive and neuropsychiatric deficits. At present, no disease modifying treatments for HD exist, but several promising genetic, small-molecule and cell-replacement strategies are in, or close to, clinical trial [1]. Undertaking large clinical trials in a rare disease is challenging as resources are limited. Furthermore, some emerging disease-modifying approaches are highly complex, placing an imperative on conducting efficient trials that minimise participant numbers. Achieving trials with smaller numbers of participants is dependent on sensitive, objective and reliable outcome measures not dependent on rater judgement. Although

some objective outcome measures have been tested for motor and cognitive deficits in HD [2], many are still based on subjective clinical assessment [3] and there are no validated measures for core behavioural features such as apathy.

Apathy (a deficit in goal directed behaviour) [4] presents up to 10 years before motor onset in HD and worsens alongside disease progression [5]. Goal directed behaviour depends on many cognitive processes, including option generation and selection, planning and sequencing, assigning effort for available reward and evaluating outcome (positive and negative) [4]. Current apathy assessment tools, such as the widely-used Problem Behaviours Assessment - short form (PBA-s) [3], are vulnerable to rater bias, inter-rater variability, social context and unavailability of co-informants at interview.

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We developed a battery of objective cognitive tasks measuring the cognitive processes underlying goal-directed behaviour in HD [6,7]. We found that two novel tasks measuring evaluation of negative outcome (Persistence task), and option generation (Maze task), reliably distinguished between HD and control, and were associated with apathy scores in HD.

In this study, we aimed to evaluate their performance against established measures of disease progression in HD at distinguishing cases from controls, measuring change over time and predicting apathy scores using the PBAs.

## 2. Methods

### 2.1. Recruitment and inclusion criteria

137 participants (83 with genetically confirmed HD, and 54 age-matched controls) were recruited at 4 Enroll-HD [8] centres (Cardiff, Manchester, Paris and Münster). HD participants were in disease stages I or II, according to UHDRS Total Functional Capacity (TFC) staging. The study was approved by the Research Ethics Council for Wales (15/WA/0428).

### 2.2. Data collection

All participants completed assessments at baseline and 12 months. Assessments included established measures used in the ENROLL-HD observational study [8]; the Unified Huntington's disease rating scale (UHDRS), TFC and Total Motor score (TMS), Symbol Digit Modalities task (SDMT), Stroop Word Reading task (SWR), PBAs, in addition to the Persistence and Maze tasks. Guidance on novel task administration was translated across languages using a forward-backward translation loop. Motor and functional assessments were administered by experienced neurologists or by appropriately trained clinical/research staff. Composite disease progression score (cUHDRS) was calculated according to the equation formulated by Schobel et al. [9].

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

The chronology of assessments was the same at baseline and 12 months.

### 2.3. Gold standard apathy assessment

The PBAs [3] is a semi-structured clinical interview covering 11 neuropsychiatric symptoms relevant to HD, and scores participants on both severity and frequency of these symptoms (each rated 0–4) over the preceding month. We used the product of severity and frequency scores (maximum score = 16) for the apathy item (PBAs-apathy).

### 2.4. Novel assessments

Both tasks have been described previously.[6,7] They were performed in a distraction-free environment on a lenovo ThinkPad laptop and programmed in E-Prime 2.0. Participants sat a comfortable distance from the screen.

#### 1) Maze Task (Option Generation and Selection)

The task was designed to mimic game play in a text based role-playing game. Participants were told they would explore a new world and were shown 15 scenarios with instructions on screen (and also read

aloud by the researcher); for example “You are alone next to a red house. What would you like to do next?” As soon as the participant started to respond, the researcher stopped the timer and entered the response. The outcome measure was the mean response time in milliseconds.

#### 2) Persistence Task (Sensitivity to Negative Outcome)

Participants were asked to compete in a car race against a competitor, and told that pressing the spacebar repeatedly speeds their car up, whilst pressing “Q” allows them to end the task at any point. Figures for distance travelled and checkpoints passed were shown prominently on screen (in addition to task instructions). The opponent is consistently faster – the outcome measure is latency to quit the task in seconds. The task ends after 10 min if participants do not choose to quit.

### 2.5. Data analysis

Generalised linear models (GLMs) were constructed to determine group differences (HD versus control) and longitudinal change over 12 months in HD cases. Receiver Operating Characteristics (ROC) analyses were performed both cross-sectionally and longitudinally to assess the task's ability to predict PBAs-apathy score.

All analyses were conducted in R, an open-source statistical software package. Shapiro test of residuals, Durbin-Watson and Goldfeld-Quandt tests were used to test for assumptions underlying the regression models: normality of residuals, autocorrelation and homoscedasticity. When the assumptions were not met an alternative generalised linear model (GLM) was used. Missing data were removed in a pair-wise fashion.

Anonymised data is available on reasonable request.

## 3. Results

### 3.1. Participant Demographics

Average CAG repeat length of HD participants was 43 (range 38–62), and there were no significant differences in average age, gender or years of education between cases and controls (Table 1).

### 3.2. Distinguishing between cases and controls

All established clinical variables (TMS,TFC, SDMT, SWRT, PBAs- apathy) reliably distinguished between cases and controls across all time points. GLMs demonstrated that the Persistence ( $p = 4.8 \times 10^{-5}$ , estimate = 0.0057) and Maze ( $p = 0.0056$ , estimate =  $4.2 \times 10^{-4}$ ) tasks both significantly distinguished between cases and controls.

### 3.3. Sensitivity to change over time

GLM revealed that the only measure to significantly change across 12-months was the Maze task ( $p = 0.0044$ , estimate = 0.19) (Fig. 1).

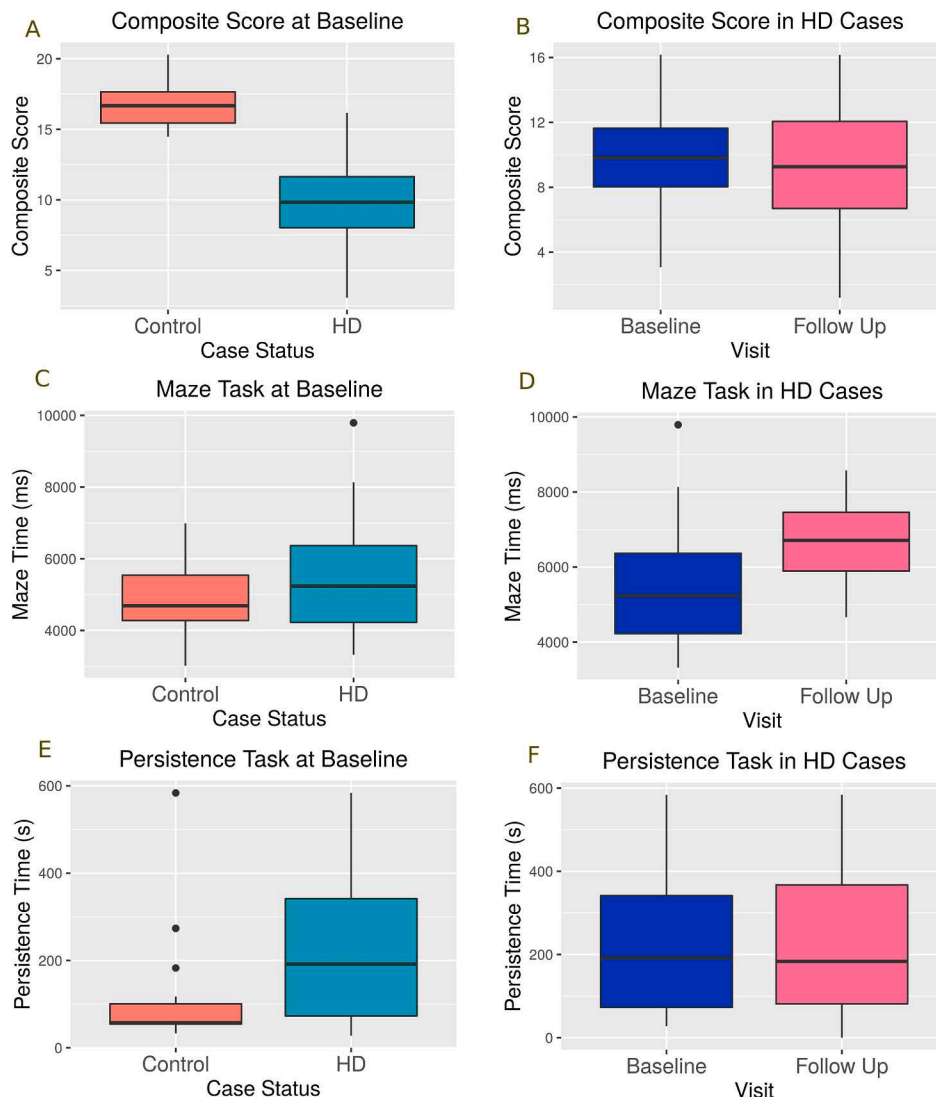
### 3.4. Association of novel tasks with PBA- apathy

Multiclass ROC analysis suggested that the Persistence task was a better predictor of PBA- apathy across all time points (AUC = 0.7619) than the Maze task (AUC = 0.72). At baseline, the Persistence task was very good at predicting PBA apathy (AUC = 0.86), and this decreased only slightly at follow up (AUC = 0.8075). Conversely, the Maze task performed better at follow up (AUC = 0.93) than at baseline (AUC = 0.67).

**Table 1**  
Participant demographics and CAPIT beta measures.

	HD Cases		Controls	
	Baseline	Follow-Up	Baseline	Follow-Up
Age	52.31 (23–78)	–	53.25 (26–71)	–
Sex	29/83 female	–	27/54 female	–
Years of Education	14.0 (9–12)	–	14.3 (9–24)	–
Total Functional Capacity	9.89 (5–13)	9.49 (3–13)	12.98 (0–12)	13 (13)
Total Motor Score	29.03 (1–68)	32.91 (1–67)	0.96 (0–6)	0.82 (0–6)
Symbol Digit Modality Task	30.36 (4–59)	28.17 (5–50)	49.83 (23–81)	53.79 (33–83)
Stroop Word Reading Task	62.59 (34–100)	61.84 (23–103)	98.08 (59–130)	101.03 (64–140)
Composite Score	9.7 (3.07–16.17)	9.09 (1.2–16.16)	16.77 (14.47–20.28)	17.32 (14.86–20.38)
PBAs Apathy Score	2.71(0–12)	2.62 (0–12)	0.64 (0–6)	0.08 (0–2)
Persistence(s)	233.38(27.75–584)	239.47 (0–584)	104.67 (33–583.75)	127.42 (0–273.8)
Maze(ms)	5491.55 (3320–9792)	6620.94 (4663–8576)	4877.84 (3017–6988)	5796.33 (3533–7463)

HD - Huntington’s disease; CAPIT - Core Assessment Program for Intracerebral Transplantation; PBAs -Problem Behaviours Assessment-short form. Baseline – Month 0, Follow-Up – Month 12.



**Fig. 1.** 1A),1C),1E) – Comparison of Huntington’s disease patients and healthy controls at baseline. 1A) Composite score derived from Schobel et al. [9]; 1C) Maze Task and 1E) Persistence Task. 1B), 1D), 1F) – Change from baseline to follow up in Huntington’s disease patients. 1B) Composite score derived from Schobel et al. [9]; 1D) Maze Task and 1F) Persistence Task. Boxplots show median and interquartile range. Baseline – Month 0, Follow-up – Month 12.

**4. Discussion**

In this work we found good discrimination between cases and controls using established and novel assessments, however, the Maze task

was the only measure in this study to detect change over 12 months in HD patients, including the cUHDRS [9].

ROC analyses revealed that the Persistence task showed good prediction of PBA apathy scores, whilst the Maze task performed less well.

One explanation may be that apathy as defined by the PBAs and the elements of goal directed behaviour thought to be measured by the Maze task, are fundamentally different constructs with dissociable neural correlates. The Maze task requires individuals to generate new ideas, an ability underpinned by executive control and creative thought [10], it may provide a measure of creativity. Creative cognition is thought to comprise flexible and persistent components, both modulated by dopaminergic systems in frontal-striatal brain circuits [10]. These frontal-striatal networks, modulated by dopamine, are also heavily implicated in the apathetic symptoms of HD [11], suggesting that creativity and apathy in HD may be interrelated. Alternatively the Maze task may measure deterioration in a cognitive process before the PBAs- apathy test can detect it. This is supported by the insensitivity to change over time of the PBAs- apathy seen in our study.

The failure to record change over time in the Persistence task may reflect the nature of this task: once participants have performed the task once, they become aware that the goal of the task is to determine latency to quit. When asked to perform it again, they are understandably unwilling to keep competing when there is no prospect of them winning. Nevertheless, the Persistence task was still able to distinguish cases from controls at both time points, confirming our previous findings of a deficit in response to negative outcome in HD [7]. Other groups have also reported impairments in negative emotion recognition [5] and also deficits on a task of learning from losses [12] in HD participants prior to motor onset, demonstrating that insensitivity to negative stimuli has potential to be a useful cross-sectional measure even in very early disease.

In this study the Maze task was the only sensitive measure of HD clinical progression over 12 months, including the cUHDRS. Whilst studies such as TRACK-HD [5] have reported change compared to controls in a larger dataset on the UHDRS, the authors did not report change within the HD cohort. An analysis of the first 100 subjects in the ENROLL-HD database does not show change on the cUHDRS from baseline to first follow-up (unpublished data, R script available in [supplementary data](#)). Currently, the lack of objective and sensitive outcome measures across the range of symptom modalities is a significant barrier to the development of therapeutics for HD and other rare neurodegenerative disorders. The fact that change was detectable in a comparatively small cohort, using 3 different languages, is highly encouraging, although further work is needed to replicate the longitudinal performance of the Maze task at varying stages of disease, and validation in other languages is also a priority. This study emphasises the importance of generating more reliable and sensitive tools to improve the ability of clinicians to track disease progression and facilitate clinical trials of new therapeutics.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.prdoa.2022.100168>.

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