Huntington's disease patients display progressive deficits in hippocampal-dependent cognition during a task of spatial memory

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Abstract

Background: Cognitive disturbances occur early in Huntington’s disease (HD) and place a significant burden on the lives of patients and family members. Whilst these impairments are typically attributed to deterioration of the frontal-striatal pathways, accumulating evidence suggests that hippocampal dysfunction may also contribute to such impairments. Here, we employ a novel spatial memory task that has previously been shown to elicit impairments in individuals with focal hippocampal lesions, as a means to further investigate the role of hippocampal dysfunction in HD.

Method: Sixty-four individuals participated in the study, including 32 healthy controls, 11 patients with diagnosed HD and 16 premanifest HD gene carriers. We also included an additional control group of 5 individuals with focal unilateral basal ganglia lesions. Participants undertook a task that measured perception and short-term spatial memory using computer-generated visual scenes.

Results: HD patients experienced significant impairments in spatial perception and memory, which strongly correlated with disease burden score (DBS). Premanifest gene carriers performed at a similar level to healthy controls throughout all aspects of the task indicating that the effects seen in the HD patients represent a deterioration in function. Interestingly, basal ganglia lesion patients were not impaired in any aspects of the task.

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1. Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease that typically develops in early to middle adulthood. Whilst traditionally considered a movement disorder, cognitive impairments are a prominent feature of the disease and can be evident up to 15 years prior to the onset of motor disturbances (Paulsen, Langbehn, & Stout, 2008). Such deficits typically consist of impaired “executive functions” such as attention, planning and cognitive flexibility (Harrington, Smith, Zhang, Carlozzi, & Paulsen, 2012; Lawrence et al., 1996; Montoya, Price, Meneur, & Lepage, 2006). In addition, deficits in emotion recognition (Johnson et al., 2007; Mason et al., 2015), processing speed (Beglinger et al., 2012) and reasoning (Giralt, Saavedra, Alberch, & Perez-Navarro, 2012) are also common. The cognitive features of HD are generally attributed to neuronal dysfunction in cortico-striatal circuits.

Recent evidence suggests that HD patients also have problems with spatial navigation and remembering specific locations within a given environment (Brandt, Shpritz, Munro, Marsh, & Rosenblatt, 2005; Majerová et al., 2012; Pirogovsky et al., 2015), although the neural underpinnings of these deficits are unclear. Decades of research has highlighted the importance of the hippocampus in spatial navigation. For example, studies on the rodent hippocampal formation led to the seminal discovery of “place cells”, neurons that fire in relation to a rodent’s specific location within an environment regardless of its orientation (O’Keefe, 1976). These findings led to the suggestion that the hippocampus forms a so-called cognitive map of the spatial environment. Support for this idea comes from human studies which have demonstrated that damage to the hippocampus impairs spatial memory, primarily affecting allocentric rather than egocentric spatial processing (i.e., the recall of locations relative to the environment as opposed to relative to the body.) (Maguire, Burke, Phillips, & Staunton, 1996; Smith, 1988) In addition, functional imaging studies have shown that the hippocampus is activated during spatial navigation of virtual environments (e.g., Aguirre, Detre, Alsop, & D’Esposito, 1996; Hartley, Maguire, Spiers, & Burgess, 2003) and that hippocampal volume correlates with navigational performance (Bobbot, Iaria, & Petrides, 2004; Burgess, Maguire, & O’Keefe, 2002; Maguire et al., 2000, 2006).

Given that hippocampal volume is reduced in HD during the early stages of the disease (Rosas et al., 2003), it is possible that the spatial memory deficits in HD are indicative of hippocampal dysfunction. However, it is also possible that such deficits are related to striatal dysfunction as studies show that the caudate nucleus, the primary site of degeneration in HD, is also implicated in spatial navigation. Evidence suggests that activation of the caudate nucleus occurs after repeated exposure to a given environment (Chersi & Burgess, 2015; Knowlton, Mangels, & Squire, 1996) and this has led to the idea that the hippocampus is associated with rapid acquisition of spatial information whereas the striatum is more associated with incremental response learning (O’Keefe & Nadel, 1978).

Evidence in support of hippocampal mediated cognitive deficits in HD comes from mouse models of the disease which display impaired spatial learning during navigation tasks such as the Morris Water Maze (Lione et al., 1999), alongside aberrant hippocampal synaptic plasticity (Murphy et al., 2000) and reduced neurogenesis (Gil et al., 2005; Lazic et al., 2006; Phillips, Morton, & Barker, 2005). In HD patients, our group has recently shown that performance on two hippocampal-based tasks, the CANTAB Paired Associates Learning (PAL) task and the computerised human analogue of the Morris Water Maze is impaired in HD. Early stage HD patients (with a Total Functional Capacity score ≥ 10) were impaired on both tasks compared with age and sex matched controls. Such deficits also correlated with estimated years to diagnosis in premanifest HD patients (i.e., gene carriers who currently do not display sufficient signs or symptoms to warrant a clinical diagnosis) (Begeti, Schwab, Mason, & Barker, 2016). A finding that has recently been replicated by another group (Glikmann-Johnston, Carmichael, Mercieca, & Stout, 2019).

However, our original study was unable to show unequivocally that poor performance on these tasks was exclusively due to hippocampal dysfunction, as already stated, other brain regions known to be impaired in HD, such as the striatum or frontal cortex, have been shown to contribute to deficits on these tests in other diseases. For example, a functional imaging study has shown that activation of the caudate nucleus positively correlates with performance on the PAL in healthy volunteers and patients with Alzheimer’s disease (Gould et al., 2005) and the Morris Water Maze has also been shown to involve other brain regions including the striatum (Woolley et al., 2013).

In order to address this issue, the current study used a recently developed hippocampal-dependent task (Hartley et al., 2007), to more completely evaluate hippocampal function in premanifest and early stage HD. The spatial memory component of this task, which measures allocentric spatial processing, has been shown to elicit deficits in individuals with focal hippocampal lesions (Hartley et al., 2007) and Alzheimer’s disease (Bird et al., 2010), but not in those with fronto-temporal dementia. In addition to the main experimental group, we administered the task to a group of individuals with focal lesions to the basal ganglia to minimise
the possibility that any impairments observed were driven by striatal rather than hippocampal dysfunction.

All of this work seeks to better understand the nature of cognitive deficits in HD alongside their neural underpinnings, which is important given that patients and their families often find that the cognitive aspects of the disease are more debilitating than motor features (Center for Drug Evaluation and Research (CDER) US Food and Drug Administration (FDA), 2016).

2. Method

We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

A summary of the participants’ demographic details can be found in Table 1. There were 64 participants in this study, comprising 11 manifest HD patients, 16 premanifest HD gene carriers, 32 healthy controls and 5 individuals with focal basal ganglia lesions due to stroke or astrocytoma.

HD patients were recruited from the John Van Geest Centre for Brain Repair, Cambridge. All had genetic confirmation of their gene status with a CAG repeat expansion >36. Patients were classified as either premanifest (Unified Huntington’s Disease Rating Scale (UHDRS) score <5) or early disease stage (UHDRS >5) by an experienced neurologist with a comprehensive knowledge of HD. A disease burden score (DBS) was calculated for each participant using the formula ([CAG – 35.5]*age) (Penney, Vonsattel, Macdonald, Gusella, & Myers, 1997).

Control participants included partners of patients or individuals recruited from the local community via advertisement. They were screened for any ongoing neurological or psychiatric disorders and were excluded if they had a family history of HD, regardless of whether they had undergone genetic testing for the disease or not.

Basal ganglia lesion patients were recruited from the Cognition and Brain Sciences Unit’s focal lesion volunteer panel, the Cambridge Cognitive Neuroscience Research Panel (CCNRP). These patients have all suffered from a focal, non-traumatic brain injury caused by either a stroke or a tumour, within the last 5 years (see Table 2).

Informed consent was obtained from all participants in accordance with the Declaration of Helsinki and the study was approved by the Cambridge Regional Ethics Committee and the R&D Department at Addenbrooke’s Hospital.

2.1. Neuropsychological assessments

Assessments were administered at the John Van Geest Centre for Brain Repair, either subsequent to their routine clinic visit or during a separate appointment, with the exception of the basal ganglia lesion patients who received a home visit. The task was administered using an A4 booklet format, which included written instructions. At the beginning of each subtask there were three practise items, for which the experimenter provided verbal feedback if necessary. The subtasks were presented in the same order for each participant. The

| Table 1 – Demographics of participant groups. |
|---------------------------------------------|
| Gender (M:F) | Controls | HD | All | Premanifest | Manifest |
|---------------------------------------------|
| Average age | 15:17 (n = 32) | 9:18 (n = 27) | 6:10 (n = 16) | 3:8 (n = 11) |
| 49.6 (11.9) | 49.5 (12.2) | 48 (10.3) | 54.7 (13.1) |
| (n = 32) | (n = 27) | (n = 16) | (n = 11) |
| Premorbid IQ (NART) | 114.8 (6) | 114.7 (7.9) | 114.1 (8.6) | 115.3 (7.1) |
| (max score 129) | (n = 17) | (n = 26) | (n = 15) | (n = 11) |
| MMSE (max score 30) | ND | 28.5 (1.5) | 28.8 (1.6) | 28.3 (1.7) |
| Depression (BDI) | ND | (n = 21) | (n = 11) | (n = 10) |
| (max score 63) | | (26–30) | (26–30) | |
| CAG repeat length | N/A | 41.5 (3.2) | 40.8 (1.5) | 42.7 (5) |
| (n = 22) | | (n = 13) | (n = 9) | (n = 9) |
| UHDRS | ND | 8.8 (11.4) | 1.5 (1.7) | 14.9 (6.3) |
| Motor score (max score 124) | (n = 27) | (n = 16) | (n = 11) | (n = 11) |
| Disease Burden Score (DBS) | ND | 289.1 (76.53) | 255 (53.7) | 337.9 (78.2) |
| (n = 22) | | (n = 13) | (n = 9) | (n = 9) |

| *Indicates a significant difference (p < .001) when compared with premanifest patients. |

Age and task scores are given as mean (±standard deviation). ND, not done. N/A, not available.
The Four Mountains Task is a recently developed test of spatial memory (available from http://fourmountains.org.uk/, The Four Mountains Task is a recently developed test of spatial memory (available from http://fourmountains.org.uk/).

2.2. Four Mountains Task

Table 1).

completed for a number of participants including controls (see the additional tests (such as the BDI, MMSE or NART) were not carried out. Due to time constraints or patient fatigue, some of the additional tests (such as the BDI, MMSE or NART) were not completed for a number of participants including controls (see Table 1).

2.2. Four Mountains Task

The Four Mountains Task is a recently developed test of spatial memory (available from http://fourmountains.org.uk/). Participants are shown an image of a computer-generated landscape in an A4 booklet. The landscape depicts four hills of varying shapes and sizes placed at different locations around the focal point of the image (Fig. 1).

Either simultaneously (“perception” trial) or following a 2 sec delay (“memory” trial), participants are then presented with an array of four landscapes, arranged in a 2 × 2 grid, and asked to identify which picture contains the original landscape from a different viewpoint.

Each incorrect picture represents one of the following “foils”:

- Spatial foil: The spatial layout (the position of the hills) has been changed, but the order of the hills around the centre is maintained.
- Configural foil: The spatial layout remains largely intact, but the order of the hills around the centre is changed.
- Elemental foil: The spatial layout remains largely intact, whereas the shape or size of one of the hills is changed.

A non-spatial matching task acts as an internal control, during which the four response pictures all contain the original landscape but differ according to the prevailing conditions (weather, time of day, time of year). Participants must identify the picture taken under the same prevailing conditions as the probe landscape.

Both spatial and non-spatial blocks include 15 “perception” trials and 15 “memory” trials. Each trial begins with 3 practise items and feedback is provided as necessary. During the test items, a neutral prompt is given after 30 sec if no response is made and after 1 min participants are encouraged to make a guess. Measures recorded for this task include the total number of errors made and the type of errors made in the spatial tasks.

2.3. Statistical analysis

IBM SPSS statistics v23 was used to conduct the statistical analysis and the graphs for the figures were created using GraphPad Prism Software v7.0.

2.4. Demographics

Group differences in age and IQ were evaluated using a one-way ANOVA followed by post-hoc analysis with an independent sample t-test. Performance on the Mini Mental State Examination (MMSE), the Unified Huntington’s Disease Rating Scale (UHDRS) and the Beck Depression Inventory (BDI) was compared between premanifest and manifest patients using an independent samples t-test.

2.5. Performance on the Four Mountains Task

A 4 × 4 ANOVA with group (premanifest HD, manifest HD, basal ganglia lesion or control) as the independent variable and condition (spatial perception, spatial memory, non-spatial perception and non-spatial memory) as the dependent variable was conducted to determine whether disease affected performance on the Four Mountains Task. To assess the subtask performance of each participant group (i.e., controls vs premanifest, controls vs manifest, premanifest vs manifest), post-hoc independent sample t-tests were then performed. Finally, a Pearson’s correlation coefficient (r) was used to measure the strength of the association between task scores and DBS.

The ethics approval under which this study was conducted does not allow individual anonymised study data to be archived. Data are available on request from Kate Harris (lead author) or the Cambridgeshire 2 ethics committee, Cambridge UK. Access is restricted to individuals named on the ethics application. No part of the study procedures or analysis was pre-registered prior to the research being conducted.
3. Results

3.1. Demographic characteristics

The characteristics of each participant group are shown in Table 1. No significant differences were found between controls, basal ganglia lesion patients and HD patients in terms of age and premorbid IQ.

The mean score for both HD groups on the MMSE was 28 out of 30, which lies within the normal range. Three patients had a score below the clinical cut-off of 23 (indicating global cognitive impairment) and these patients were therefore excluded from the analysis as it seemed that they had not understood the task when their scores were examined. As expected, the manifest group had a score of 29 or greater in the MMSE, indicative of normal cognitive function. BDI scores did not differ between the basal ganglia lesion group and the HD group.

4. Four Mountains Test

Scores in each subtask for each participant group are shown in Fig. 2 and Table 3.

A mixed ANOVA with a Greenhouse-Geisser correction indicated that there was a significant main effect of “Group” on the Four Mountains Task $[F (3, 60) = 9.735, p < .001]$ but with no significant interaction between disease and subtask $[F (2.7, 162) = 1.939, p = .132]$, this indicates that performance increases or decreases between different disease groups (premanifest HD, manifest HD, focal lesion group and controls) but the pattern of responding remains the same.
Fig. 2 – Performance on the Four Mountains Test. (A) Average scores on each subtask for HD gene carriers (premanifest and manifest combined) and control groups. Manifest HD patients perform significantly worse than controls in spatial perception (B), spatial memory (C), non-spatial perception (D) and non-spatial memory (E). Individual scores are shown as squares. Error bars indicate the standard deviation. HD n = 27; Controls n = 32; Basal ganglia lesion n = 5.
Table 3 – Four Mountains Task scores.

|                      | Controls      | Basal ganglia lesion | HD            |
|----------------------|---------------|----------------------|---------------|
|                      | All           | Premanifest          | Manifest      |
| Spatial perception   | 11.8 (2.1)    | 10.6 (1.6)           | 9.7 (3.4)*    |
|                      |               | 11.2 (1.9)           | 11 (2.8)      |
|                      |               | 11.3 (2.3)           | 8 (3.5)**     |
| Spatial memory       | 11.1 (2.5)    | 10.7 (1.5)           | 8.5 (3)*      |
|                      |               | 11.2 (4)             | 9.6 (2.9)     |
|                      |               | 10.8 (8)             | 6.9 (2.3)**   |
| Non-spatial perception| 5.3 (2.8)    | 5.2 (2.6)            | 9.9 (2.6)*    |
|                      |               | 5.1 (2)              | 10.7 (2.5)    |
|                      |               | 5.3 (3)              | 9 (3)*        |

Score are mean (standard deviation). Maximum score = 15.

***Indicates a significant result (p < .001) compared with controls.
*Indicates a significant result (p < .05) compared with controls.
Indicates a significant result (p < .05) compared with premanifest patients.
Indicates a significant result (p < .05) compared with basal ganglia patients.

Post-hoc analysis using an independent sample t-test indicated that while performance of premanifest patients did not significantly differ from controls in any of the subtasks (p > .05), manifest disease patients scored significantly worse than controls on all subtasks [spatial perception (t (41) = 4.24, p < .001, d = 1.30); spatial memory (t (41) = 4.88, p < .001, d = 1.73), non-spatial perception (t (41) = 2.13, p = .038, d = .73) and non-spatial memory (t (41) = 2.82, p < .007, d = .89)]. Manifest patients also scored significantly worse than premanifest patients in spatial perception (t (25) = 2.45, p = .021, d = .94) and spatial memory (t (25) = 2.52, p = .018, d = 1.01) subtasks only. Finally, manifest patients scored significantly worse than basal ganglia lesion patients in the spatial memory task (t (14) = 3.00, p = .010, d = 1.71). It was also investigated whether there was a difference in the pattern of foil (error) responses chosen by the different groups, but an ANOVA showed there was no significant group by type interaction (data not shown).

To investigate the extent, if any, whether the scores on the Four Mountains Test were influenced by disease burden score (DBS) we calculated Pearson’s correlation coefficient (see Fig. 3). For this analysis we grouped together premanifest and manifest patients, although it should be noted that five HD gene carriers could not be included in the analysis because the CAG repeat length was unknown. Pearson’s correlation coefficient (r) showed a strong significant negative correlation between DBS score and both spatial perception (r = −.79, n = 22 p < .001) and spatial memory scores (r = −.71, n = 22 p < .001) and a weaker significant correlation with non-spatial memory (r = −.54, n = 22 p = .008). In contrast, DBS scores did not correlate with non-spatial perception (r = −.31, n = 22 p = .712).

5. Discussion

5.1 Spatial perception and memory

We have demonstrated that HD patients show impairment in both the spatial perception and memory subtasks of the Four Mountains Test. The degree of the impairment for the spatial memory subtask was of a similar magnitude to studies of individuals with focal hippocampal lesions, who scored between 5/15-8/15 (see Hartley et al., 2007), and with patients exhibiting early Alzheimer’s disease, where extensive hippocampal dysfunction is known to occur, who scored on average 6/15 (see Bird et al., 2010).

Whilst this suggests that hippocampal dysfunction underlies the observed deficit in HD patients, it is also possible that the caudate nucleus, which undergoes early degeneration in HD, also contributed to deficits. However, previous studies have shown that the caudate nucleus mediates incremental, stimulus-response learning of a spatial scene, which would not have been required in the current task which comprised single-response trials. Furthermore, fMRI studies have shown that the caudate nucleus is activated during egocentric, rather than allocentric spatial tasks (Boccia, Nemmi, & Guariglia, 2014). The current task required participants to use allocentric spatial strategies (to recognize an object’s location when viewed from a different point of view), which has been shown to require hippocampal function (Hartley et al, 2007). The shift of viewpoint deters participants from making a decision based on egocentric strategies. To detour visual matching strategies, foils were presented in addition to the target image, in which the size, shape or location of the mountains were altered, but local topographical features (lighting, colours and weather conditions) were the same as the target image. Furthermore, these topographical features differed in the foils/target image compared to the sample image, to further discourage visual strategies.

Based on this, it can be deduced that the striatum would not be required for the Four Mountains spatial task and, consequently, the deficits observed in the current study are theoretically more consistent with hippocampal dysfunction. Indeed, we went on to demonstrate that in a small group of individuals with heterogeneous focal basal ganglia lesions we did not find any deficits in the spatial subtasks of the Four Mountains Test. This supports a previous study, which showed that in healthy volunteers, performance on the spatial subtask of the Four Mountains test correlated with the volume of hippocampal/para-hippocampal areas but, crucially, not the volume of the caudate nucleus (Hartley & Harlow, 2012). However, it is important to note that due to the small size of the basal ganglia group in the current study, the results should be interpreted with caution. Furthermore, in contrast to the HD patients, the basal ganglia lesion patients had unilateral lesions and therefore the contralateral side of the basal ganglia may have preserved function.

Interestingly, a recent functional imaging study has reported activation of both the hippocampus and striatum...
after single-trial learning during a route recognition task, thereby challenging the assumption that the caudate nucleus only becomes involved after repeated training (Voermans et al., 2004). Furthermore, in healthy volunteers, there was an interaction between the caudate nucleus and the medial temporal lobe during the navigation task, which was reduced in patients with HD (Nopoulos et al., 2010).

Interestingly, the performance of HD patients in the route recognition task was nearly equal to that of controls, leading the authors to conclude that the hippocampus could compensate for the dysfunction of the caudate nucleus. However, that tested route recognition, which in all likelihood involves different neural processes to those involved in the spatial processing task used in the current study. Nevertheless, if the striatum were to be involved in the current task, our findings would suggest that either (1) there is an upper limit to the extent that the hippocampus can compensate for impairments in the caudate nucleus beyond which behavioural differences become detectable; or (2) that concurrent degeneration of the hippocampus in HD limits its ability to compensate for any striatal deficits that only become evident in more difficult tasks.

In the current study, premanifest HD patients performed in a similar way to controls on the spatial subtasks indicating that hippocampal-dependent cognitive dysfunction is not a feature of the prodromal stages of the disease. Given the strong correlation between performance and the DBS, even in such a small sample of participants, it is apparent that hippocampal dysfunction deteriorates in a linear fashion throughout the disease. Therefore, hippocampal abnormalities may provide a marker of ongoing disease-related cognitive deterioration in HD.

It is important to note that whilst this paper focuses on striatal and hippocampal regions, other brain regions are also likely to be involved in the execution of the current task, and dysfunction in these regions could have also contributed to the impairments observed in HD patients. One such area is the parietal cortex, which is involved in processing visuospatial information and undergoes degeneration in the early stages of HD (Labuschagne et al., 2016). A recent study found that the volume of this region is associated with performance on a visual search and a mental rotation task in HD (Corey-Bloom et al., 2016). It is also important to point out that the memory trials adopted in our study employed a two second delay between the presentation of the stimulus and the target images, and this is presumed to be a test of short-term memory. However, this delay period may in fact be measuring attention span and therefore future studies should increase the length
of this delay to ensure that the stimulus is indeed properly encoded in short-term memory.

### 5.2. Visual perception and memory

It is noteworthy that, unlike the hippocampal lesion patients in Hartley et al. (2007), the HD patients participating in our study also scored significantly worse than controls in the non-spatial subtasks of the Four Mountains Test. Similarly, patients with Alzheimer’s disease (AD) showed impairments in non-spatial perception in addition to their impairments in spatial perception and memory, see Bird et al. (2010). Those authors suggest that deficits in the non-spatial task may have been due to confusion caused by the change in rules when switching from the spatial to non-spatial tasks. This is certainly plausible with regard to the current study, since HD patients have difficulties in set shifting (i.e., in amending their strategy in response to a change in instructions) (Lawrence et al., 1996), which is presumed to result from frontal lobe dysfunction. To test this theory, non-spatial subtasks would need to be administered in isolation to AD and HD patients to verify that a true deficit exists.

It is also impossible to rule out the fact that a general lack of understanding of the Four Mountains Test might have caused global deficits in performance. However, although it is a crude measure of cognitive function, the Mini Mental State Examination (MMSE) scores did not correlate with performance in any of the subtasks except that those HD patients that scored in the demented range of the MMSE had scores that were markedly worse suggesting that they had not understood the task.

Disturbances of visual perception are frequently reported in many chronic CNS neurodegenerative disorders and although this has been understudied in HD, there is evidence of dysfunction in the visual pathways in both HD patients and HD animal models. For example, manifest HD patients, but not premanifest gene carriers, are impaired on the Benton Judgement of Line Orientation Test, a measure of visuospatial ability (Oepen, Doerr, & Thoden, 1981). Furthermore, HD patients have been shown to exhibit abnormalities in visually evoked potentials (Corey-Bloom et al., 2016) and to have reduced grey matter volume in the primary visual cortex (Beglinger et al., 2005). Therefore, it is possible that the impairments observed in non-spatial tasks are a reflection of impairments in visual perception in the current study, and this should be directly addressed in future work.

In conclusion, we have shown that HD patients demonstrate deficits in a hippocampal-dependent task of spatial perception and memory as well as more widespread deficits in visual perception and memory. Interestingly, these cognitive deficits appear to be independent of striatal impairments given that a small array of patients with specific basal ganglia lesions did not exhibit impairments on any of the tasks.

### 6. Clinical relevance

The ability to remember the locations of objects and buildings and to successfully navigate through familiar environments is a fundamental requirement of everyday life. Deficits in these abilities are known to negatively impact the lives of individuals with Alzheimer’s disease and Parkinson’s disease (Gazova et al., 2012). A better understanding of the nature of cognitive deficits in HD will be of major benefit to both patients and those who look after them. Until recently, there has been a focus on the deficits related to corticostrial circuitry, but the present study highlights the importance of investigating the role of extra-striatal brain regions. There are currently no treatments targeting the cognitive aspects of HD, but there is an urgent need for this because HD patients and their families often report the cognitive symptoms to be the most debilitating aspect of the disease. A better understanding of the neurological underpinnings of such cognitive impairments, provided by the current research, could ultimately help with the design of future treatments as a number of such approaches are now entering the clinic including a trial at our own centre (e.g., https://www.fiercebiotech.com/biotech/eip-bags-cash-to-trial-ex-vertex-drug-dementia-huntington-s).

### CReditT authorship contribution statement

Kate L. Harris: Formal analysis, Writing - original draft. Matthew Armstrong: Data curation. Rachel Swain: Data curation. Sharon Erzinclioglu: Data curation, Writing - review & editing. Tilak Das: Data curation. Neil Burgess: Writing - review & editing. Roger A. Barker: Conceptualization, Writing - review & editing. Sarah L. Mason: Conceptualization, Methodology, Supervision, Validation, Writing - review & editing.

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