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Visual Working Memory Impairment in Premanifest Gene-Carriers and Early Huntington's Disease

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Abstract. Working memory deficits have been found in Huntington's disease (HD) and in a small group of premanifest (PreHD) gene-carriers. However, the nature and extent of these deficits are unknown. In a large cross-sectional study, we aimed to determine the degree of visuospatial working memory dysfunction across multiple stages of HD. Specifically, visuospatial working memory capacity and response times across various degrees of difficulty were examined, as well as the relationship between visuospatial working memory and motor dysfunction. We examined 62 PreHD-A gene-carriers (>10.8 years from estimated disease onset), 58 PreHD-B gene-carriers (<10.8 years from estimated disease onset), 77 stage-1 HD patients (HD1), 44 stage-2 HD patients (HD2), and 122 healthy controls. Participants viewed coloured squares (in sets of 3, 5 and 7) on a screen and were to decide whether on a subsequent screen the encircled square has changed colour. Accuracy and response times were recorded. Compared to controls, significant group differences in visuospatial working memory capacity (accuracy) were seen in PreHD-B, HD1 and HD2 groups across the difficulty levels. Significant group differences on response times were found for all groups (PreHD-A to HD2) compared to controls; the most difficult level producing the only group difference in speed between PreHD-A and controls. Accuracy and speed were positively correlated only in the HD groups. These findings suggest that visuospatial working memory impairments are detectable in both premanifest and manifest HD; the manifest HD showed evidence for a "worse-worse phenomenon" whereby reductions were present in both motor speed and accuracy.

Keywords: Huntington's disease, visual working memory, cognitive dysfunction, premanifest gene-carriers

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease, which is characterised by progressive motor, psychiatric and cognitive symptoms and signs [1–4]. The mean age of disease diagnosis is between 35 and 45 years [4]. Individuals at risk of carrying the HD gene can be tested. Those who are found to have the gene but not to have clinical disease (i.e., motor) signs are referred to as premanifest gene-carriers. Many studies investigating cognition in

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HD have demonstrated progressive cognitive decline resulting in dementia [5, 6]. Cognitive decline is also detectable in the premanifest gene-carriers across a number of domains, including executive functions, memory, emotion recognition and psychomotor functions [7–9].

Working memory is a topic of recent attention as a possible marker for disease state in HD [10, 11]. Many day-to-day activities require retention, integration and manipulation of either verbally or visually presented information, referred to as verbal or visual (or visuospatial) working memory [12]. Poor working memory has been described as part of the disease course of HD. In particular, several cross-sectional studies have demonstrated that HD patients show poorer spatial or visual working memory in comparison to controls [9, 11, 13–15]. Visual working memory was also found to decline in patients with HD over 12-, 24- and 42-months [2, 3, 16].

Studies of premanifest gene-carriers have identified mild-to-moderate cognitive deficits in a range of domains, including attention, memory, psychomotor speed and executive functioning, which are among the first cognitive functions to show decline in the premanifest phase [17–23]. With regard to working memory, the evidence in premanifest HD is unclear. Some studies have reported impairments in both verbal and visual working memory [17, 24]. However, others have suggested that premanifest HD do not differ from controls in either visual or verbal working memory [19, 25]. In addition, although evidence regarding working memory decline in premanifest HD is limited, it does suggest that working memory, in particular visuospatial working memory, may be among the first cognitive functions to show decline in the premanifest phase [3, 10].

Working memory is implicated in complex brain networks whereby integrated signals received by the parietal cortex, are then projected onto the frontostriatal brain circuits which then subsequently drive motor responses [26–28]. The underlying brain regions associated with working memory, namely the caudate nucleus and putamen which lie within the frontostriatal brain circuits, are also among the primary regions implicated in the cognitive dysfunction, neurobiology and aetiology of HD [29–33]. Specifically, brain activation studies involving working memory performances in premanifest HD reported reduced functional connectivity in regions of the frontostriatal brain circuit such as the putamen and prefrontal cortex [34, 35], as well as reduced brain activity during electroencephalograph measures [36], when compared to controls. These changes were observed even in the absence of behavioural differences in working memory task performance. Structural evidence has shown that brain atrophy in premanifest gene-carriers develops prior to disease diagnosis, and it progresses during the disease course, with the most profound and earliest changes found in the caudate nucleus and putamen [9, 37–39]. Given that both cognitive dysfunction and abnormal neurobiology have been observed in HD including in premanifest gene-carriers who are more than ten years before estimated disease onset [9, 20, 22, 39], it can be expected that deficits in visual working memory would develop as the disease progresses (and the brain regions deteriorate).

In addition, motor functioning overlaps with cognitive functioning, in that both are implicated in brain structures such as the basal ganglia [40], and cognitive performance is measured through motor outputs such as verbal or button-based responses. The most sensitive assessments of early cognitive changes in HD are those with a substantial psychomotor speed component [8, 9, 22, 41]. Therefore, to better understand how HD affects cognition, it is important to distinguish, where possible, the impact of motor functioning on cognitive measures. Also, as we move toward treatment-focused studies in HD, it is necessary to understand the progression of cognitive deficits in relation to motor dysfunction. This is important since patient groups are often defined in terms of their level of motor deficits. The distinction between premanifest and manifest HD is made based on the level of motor abnormalities. For premanifest groups, stringent exclusion of motor deficits can facilitate distinctions between motor and cognitive disease effects, although subtle motor changes are not eliminated by this approach. Cognitive tasks that require minimal motor responses are also desirable in this respect.

The background presence of motor slowing also complicates the interpretation of cognitive testing in HD. One approach, to disentangle the motor and cognitive effects, is to examine the relationship between performance accuracy and response times. This relationship is often observed as a 'speed-accuracy trade-off', which refers to a strategy whereby participants use a slower, more cautious approach to ensure the accuracy of their performance. Conversely, faster responses may lead to greater inaccuracy due to being less careful or less cautious. We hypothesised that HD gene-carriers may slow their responses as a compensatory strategy in order to maintain satisfactory cognitive performance. Because we wanted to examine whether speed-accuracy trade-offs would appear in

relation to working memory performance in HD, we selected a task in which these two aspects of performance could be examined separately, allowing their relationship to be studied in the context of HD.

Using data obtained from a large multisite international and observational study known as TRACK-HD [3, 9], the current study aimed to determine, using a more detailed analysis, the degree of visuospatial working memory dysfunction in HD. Previous publications from TRACK-HD [2, 3, 9] have reported on data from the current working memory task; however this involved reporting only a single primary outcome variable (i.e., working memory capacity) with different group comparisons and using different statistical analysis techniques. Specifically, we aimed to examine visuospatial working memory impairments relating to working memory capacity and response times across multiple disease stages including both premanifest gene-carriers and those in early stage HD. In addition, and unlike the previous publications, we wanted to examine visuospatial working memory function in HD across different levels of task complexity. Furthermore, we wanted to distinguish between cognitive and motor influences in order to clarify whether working memory itself, rather than just the motor expression of this cognitive function, is affected in HD. By addressing these aims, we can obtain evidence regarding the possibility that a working memory task may be suitable as a marker for cognitive deterioration in early diagnosed or even premanifest HD.

METHODS

Participants

Three hundred and sixty-six subjects were studied as part of the TRACK-HD study [1, 3, 9]. Of these, 123 were premanifest gene-carriers, defined as genetically confirmed but without clinically evident symptoms, 120 were patients with stage 1 and 2 HD; and 123 were age- and sex-matched healthy controls. Participants were recruited from four study sites: London (UK), Paris (F), Vancouver (CAN), and Leiden (NL). Premanifest participants were included only if they did not have substantial motor signs as indicated by total motor scores of $\leq$5 points on the Unified Huntington's Disease Rating Scale [UHDRS; 42], and if they had Disease Burden Scores of at least 250 [43]. For each premanifest gene-carrier, we computed an estimate of the proximity (in years) to predicted disease onset based on CAG repeat length and current age [44]. Then, using a median split (10.8 years to expected onset) we created a *further from estimated onset group* (PreHD-A, >10.8 years to estimated onset) and a *closer to estimated onset group* (PreHD-B, <10.8 years to estimated onset). For early stage HD participants, we used Total Functional Capacity (TFC) scores from the UHDRS to differentiate between those in the HD stage 1 group (HD1, TFC scores 11–13) and HD stage 2 group (HD2, TFC scores 7–10) [45]. For information on the full cognitive assessment battery, additional examinations and detailed inclusion criteria, see Tabrizi et al. [3, 9]. In the current report, we report cross-sectional data from a visual working memory task, *Spot the Change* (SPOT).

Spot the Change task

The Spot the Change task (SPOT) was based on a visual array comparison task [46, 47]. Using a Lenovo Vantage ThinkPad tablet PC (IBM, New York), participants viewed an array of coloured squares (250 ms) on the screen, followed by a blank display (1000 ms). This was followed by a second array of coloured squares in which one of the squares is encircled. The position of the squares was unchanged between the two presentations. Participants were asked to indicate if the colour of the encircled square had changed from the first to second display. Using a mouse mounted on a stabilising wooden platform, the response "same" was to be made using the dominant thumb to indicate that the encircled square had not changed colour, and a response of "different" was to be made using the non-dominant thumb to indicate that the colour of the encircled square had changed and was therefore 'different'. "Same" and "Different" labels were attached to the mouse platform to remind subjects which thumb corresponded to which response. No feedback was provided following participant responses. Responses could be made up to 8 seconds after the beginning of the second display. Prior to starting the task, instructions and a minimum of four practice trials were given to ensure task comprehension.

In order to determine the most sensitive task condition, three levels of difficulty were used which were based on the number of coloured squares contained in the array. Ranging from easiest to hardest, they included three coloured squares (set size 3), five coloured squares (set size 5), and 7 coloured squares (set size 7). Data from the three set sizes were collected at two different visits separated by 12-months. Set sizes 3 and 5 were collected at visit 1 (baseline), and set size 7, along with set size 5 again, were collected at visit 2 (12-month follow-up). Each set size

consisted of 32 trials, and stimuli were presented at random. At the 12-month follow-up visit, set size 3 was excluded because the baseline results showed ceiling effects, and as a result we introduced a more difficult condition, set size 7. This paper is reporting on cross-sectional data from set sizes 3 and 5 (collected at visit 1) and set sizes 5 and 7 (collected at visit 2). Longitudinal data for set size 5 has been reported in our previous report; see Tabrizi and colleagues [3]. Accuracy and response time were recorded and analysed separately for each of the set sizes.

Non-response trials were recorded when a participant did not respond within the given 8-second time frame, which occurred 168 times across the groups for both visits and all set sizes (0.38% of the trials). In an additional seven trials, responses were given within 100 ms of the stimulus; these were considered to be 'pre-cognitive' or accidental responses and were excluded from the analysis. Accuracy measures were corrected for guessing by the calculation of k; a measure of working memory capacity as described by Cowan [46]. It is computed as k = set size n ([number correct hits/number of trials] + [number correct rejections/number of trials] − 1). A k (working memory capacity) value close to the set size (e.g., 3, 5 or 7) indicates good working memory capacity, whereas a k value close to or less than zero represents performances closer to chance.

Of the subjects that attended the visits, only a small number of participants failed to complete the Spot the Change task, which was nearly always due to time constraints. The task was completed at visit 1 (baseline), visit 2 (12-month follow-up), or at both visits by a total of 363/366 (99%) participants (with 1 control and 2 HD2 participants not completing the task at any of the visits and were thus excluded from the analysis). Visit 1 had a total of 355 of 366 who completed the task (97%), yielding missing data for 3 controls, 5 HD1, and 3 HD2. Of the 355 (92%) participants at visit 1, 325 participants returned for visit 2, with an additional 8 completing the task who did not do so at visit 1. Therefore, 333 out of 366 (91%) completed the task during visit 2, yielding missing data for 9 controls, 1 PreHD-A, 5 PreHD-B, 6 HD1 and 12 HD2 during this visit.

Statistical analysis

All analyses were performed using SAS v9.2 (Stata Corporation, College Station, Texas). The working memory capacity (k) data were analysed in a single regression model incorporating data from the three difficulty levels and both visits. Working memory capacity (k) was the outcome variable of interest. The main predictors were group (controls, PreHD-A, PreHD-B, HD1 and HD2) and set size at each visit (set sizes 3 and 5 at visit 1 and set sizes 5 and 7 at visit 2). Response times (RT) were considered separately for correct (correct recognitions and correct rejections) or incorrect (incorrect recognitions and incorrect rejections) trials. The distributions of RTs were highly skewed and therefore were log transformed prior to analysis to improve normalisation of these variables for statistical analysis. Similar to the analyses for working memory capacity, all RT data from both visits and from all three set sizes were analysed in a separate single regression model with RT as the outcome. The main predictors were group (controls, PreHD-A, PreHD-B, HD1 and HD2), response accuracy (correct or incorrect) and set size (set sizes 3 and 5 at visit 1 and set sizes 5 and 7 at visit 2).

Age, gender, education level and study site were included as covariates for both the working memory capacity (k) and RT models. The regression models used generalised estimating equations, which have a working assumption of exchangeability and robust standard errors [48, 49]. This allowed for cross-sectional comparison of each gene-carrier group to controls for each set size. We also examined whether groups responded differently in terms of RTs for correct versus incorrect trials.

Finally, to examine the direct relationship between accuracy and RT, we computed separate linear regression models for each set size with the mean of the log transformed RTs for each individual as the outcome measure. Because interactions require larger samples we collapsed the five groups into three groups which included controls, a premanifest group (PreHD-A and PreHD-B combined) and an early HD group (HD1 and HD2 combined). For this analysis, k and group (controls, PreHD, and early HD) were the main predictors. Again, age, gender, education level and study site were covariates. A group versus k interaction was included to allow for differences in the speed/accuracy relationship between groups to be investigated.

RESULTS

To address our primary objective of examining visual working memory, here we first describe k (working memory capacity) for each set size (3, 5 and 7) in the five groups (controls, PreHD-A, PreHD-B, HD1 and HD2). We then present RT findings per set size across five groups. Finally, we describe the relationship between RT and accuracy to further characterise the

nature of visual working memory using three groups (controls, PreHD and early HD).

Working memory capacity (k) was significantly lower for the PreHD-B, HD1 and HD2 groups at each visit for each set size (3, 5 and 7) compared to healthy controls (Table 1 and Fig. 1a and b). PreHD-A did not show a difference to controls for any set size at either visit. Set size 3 demonstrated a ceiling effect in controls and both premanifest groups (PreHD-A and PreHD-B), but this ceiling effect was not apparent for set sizes 5 and 7.

The RTs in the easiest condition, set size 3, were slower in the PreHD-B, HD1 and HD2 than in controls when answering correctly, despite the ceiling effect (Table 1 and Fig. 1c). For set size 3 incorrect responses, only the HD2 group was significantly slower than controls. The response times for correct trials on set size 5 (the moderately difficult trials) showed a relatively consistent pattern across visits, with the PreHD-A looking most similar to controls, followed by the PreHD-B group and then HD1 and HD2, with greatest slowness in the most advanced group (HD2). In contrast, response times for incorrect trials on set size 5 showed a less consistent pattern; see Table 1 and Fig. 1c, d. In the most challenging condition, set size 7, all four clinical groups (PreHD-A, PreHD-B, HD1 and HD2) were significantly slower than controls when responding correctly, but when responding incorrectly, only HD1 and HD2 were slower; see Table 1 and Fig. 1d.

Overall, across all set sizes (3, 5, and 7) response times for correct responses showed more consistent results across groups such that the PreHD-A group looked more similar to controls, followed by the PreHD-B group, and then the HD1 and HD2 groups. In contrast, the responses time for incorrect responses showed less consistency in these relationships. A statistically significant interaction between HD group and response accuracy (see p values in the rightmost column of Table 1) indicates that the magnitude of the difference between the RT in correct trials and the RT in incorrect trials (i.e., estimated RT for incorrect trials minus estimated RT for correct trials) for the group in question was different to the magnitude of this RT difference in controls. For set size 5, for example, the magnitude of the difference in RTs between correct and incorrect trials was found to be different from that in controls for both HD1 and HD2 at both visit 1 and visit 2 ($p<0.001$ in all cases). These interactions are clearly illustrated in Figs. 1c and 1d. For all set sizes and all HD groups, RTs are larger for incorrect than for correct responses. However, the difference between mean RTs for correct and incorrect responses is greatest in controls and declines with increasing severity of disease stage, with much less differentiation between RTs for the two response categories in the HD1 and HD2 groups, especially for set sizes 5 and 7.

In a separate analysis of the relationship between speed and accuracy, we found no evidence for a relationship between speed of response and accuracy for any of the set sizes in either controls or the premanifest gene-carrier group. In contrast, we did find that slower response times were related to lower accuracy levels in the manifest early HD group for all set sizes. Specifically, longer RTs were associated with less accurate responses at visit 1 for set sizes 3 and 5, and at visit 2 for set sizes 5 and 7 (all p-values <0.001; see Fig. 1e).

DISCUSSION

This study's main findings were two-fold. Firstly, when compared to controls, visuospatial working memory capacity and response times were found to be poorer in both premanifest HD gene-carriers who were within a decade of disease onset, and those in the early stages of HD. Secondly, in manifest HD, despite observing both poor working memory capacity and slower response times, the relationship between motor response speed and accuracy did not indicate a speed-accuracy trade-off, but rather we observed that longer response times corresponded to poorer performance.

From these results we conclude that working memory capacity is impaired in premanifest gene-carriers close to expected disease onset (i.e., within 10.8 years of expected diagnosis) and in stage 1 and 2 HD patients as compared to healthy controls. This is consistent across all set sizes (3, 5, and 7) and both visits. These findings confirm the presence of dysfunction in visual working memory which has previously been found in HD patients in cross-sectional studies [13, 50], and now extends these findings to premanifest HD. In the previously reported TRACK-HD study [9], cross-sectional findings on group differences for working memory capacity were reported for adjacent groups (e.g., PreHD-A vs. PreHD-B and PreHD-B vs. HD1) and not for every clinical group as compared to controls as was done in the current study. In their only comparison to controls, the authors found a significant difference on accuracy between controls and the near from onset premanifest group [9], which is similar to the current findings. Furthermore, the task used in the current study required various levels of working memory capacity as demonstrated by the three set sizes;

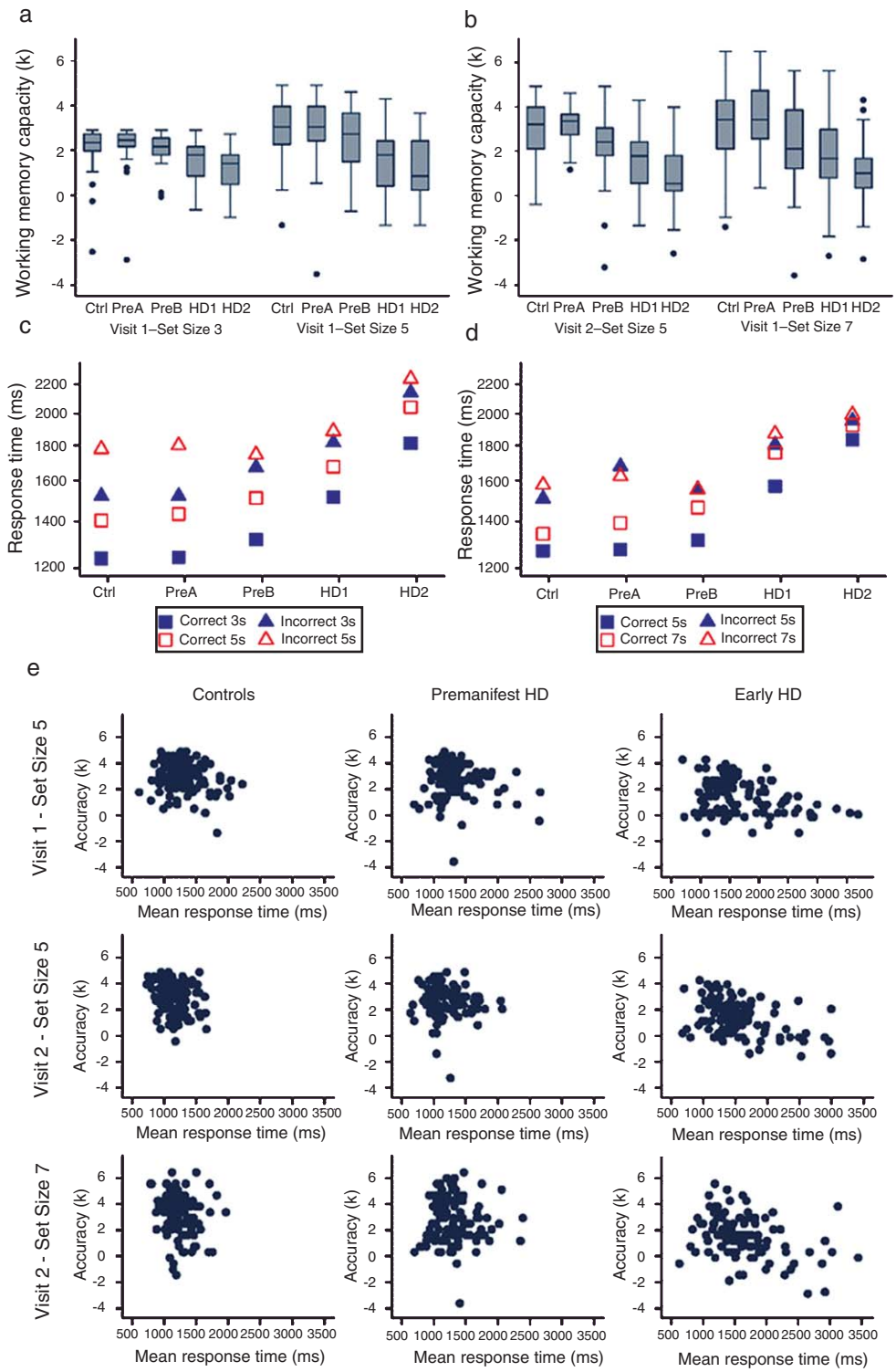

Fig. 1. Working memory capacity for set sizes 3 and 5 at visit 1 (a), and set sizes 5 and 7 at visit 2 (b) for HD gene-carriers and healthy controls. Response time for set sizes 3 and 5 at visit 1 (c) and set sizes 5 and 7 at visit 2 (d). Speed vs. accuracy for set sizes 5 and 7 (e) in controls, premanifest gene-carriers (PreHD) and patients (set size 3 not shown due to ceiling effect in controls and premanifest gene-carriers). Ctrl = healthy controls, PreA = premanifest gene-carriers far from expected disease onset, PreB = premanifest gene-carriers close to expected disease onset, HD1 = patients in stage 1 of the disease, HD2 = patients in stage 2 of the disease, Visit 1 = baseline visit, Visit 2 = 12-month visit.

Table 1
Participant characteristics and adjusted differences[a] in working memory capacity and response time for set sizes 3, 5 and 7 for HD gene-carriers compared to controls

	Number of participants	Female/male	Age (years)[b]	Education level[c]	CAG repeat length	Expected years to onset[b]	Disease duration (years)[b]
	n	*n*	mean (SD)	mean (SD)	mean (SD)	mean (SD)	mean (SD)
Controls	122	68/54	46.2 (10.1)	4.0 (1.3)	–	–	
PreHD-A	62	33/29	41.1 (8.6)	4.1 (1.1)	42.1 (1.8)	14 (3.1)	–
PreHD-B	58	33/25	40.6 (9.2)	3.8 (1.3)	44.2 (2.5)	9 (1.3)	–
HD1	77	46/31	47.2 (10.3)	3.8 (1.3)	43.8 (3.3)	–	5 (5.8)
HD2	44	19/25	51.0 (8.6)	3.3 (1.4)	43.5 (2.4)	–	8 (4.5)

	Working memory capacity (k)			Response time (% increase)[d]						
				Correct			Incorrect			Interaction[e]
	Est.	95% CI	*p*	Est.	95% CI	*P*	Est.	95% CI	*p*	*p*
Visit 1 – Set size 3										
PreHD-A	–0.04	*(–0.26 to 0.18)*	0.70	2.6%	*(–2.6 to 8.2)*	0.33	0.8%	*(–8.7 to 11.3)*	0.88	0.66
PreHD-B	–0.26	*(–0.44 to –0.07)*	0.01	7.6%	*(1.6 to 13.9)*	0.01	8.1%	*(–3.8 to 21.4)*	0.19	0.93[f]
HD1	–0.78	*(–1.01 to –0.54)*	<0.001	18.9%	*(10.9 to 27.4)*	<0.001	7.3%	*(–2.8 to 18.3)*	0.16	0.004
HD2	–0.95	*(–1.25 to –0.65)*	<0.001	39.4%	*(27.0 to 53.1)*	<0.001	30.9%	*(17.7 to 45.6)*	<0.001	0.09
Visit 1 – Set size 5										
PreHD-A	–0.26	*(–0.61 to 0.09)*	0.14	4.6%	*(–1.2 to 10.8)*	0.12	4.9%	*(–4.3 to 15.0)*	0.31	0.94[f]
PreHD-B	–0.71	*(–1.04 to –0.37)*	<0.001	8.3%	*(1.6 to 15.5)*	0.02	2.5%	*(–7.2 to 13.2)*	0.63	0.13
HD1	–1.38	*(–1.71 to –1.04)*	<0.001	14.9%	*(7.2 to 23.3)*	<0.001	1.6%	*(–7.4 to 11.4)*	0.74	<0.001
HD2	–1.45	*(–1.84 to –1.06)*	<0.001	40.1%	*(27.7 to 53.6)*	<0.001	22.2%	*(8.5 to 37.5)*	0.001	<0.001
Visit 2 – Set size 5[g]										
PreHD-A	–0.03	*(–0.31 to 0.26)*	0.87	3.1%	*(–2.2 to 8.6)*	0.26	10.6%	*(3.0 to 18.7)*	0.005	0.005[f]
PreHD-B	–0.78	*(–1.19 to –0.36)*	<0.001	4.1%	*(–2.3 to 10.9)*	0.21	1.2%	*(–8.6 to 12.1)*	0.82	0.40
HD1	–1.38	*(–1.72 to –1.03)*	<0.001	21.0%	*(13.4 to 29.2)*	<0.001	10.7%	*(2.9 to 19.2)*	0.007	<0.001
HD2	–1.92	*(–2.40 to –1.43)*	<0.001	37.1%	*(23.6 to 52.0)*	<0.001	19.4%	*(6.3 to 34.1)*	0.003	<0.001
Visit 2 – Set size 7										
PreHD-A	–0.05	*(–0.50 to 0.41)*	0.85	5.5%	*(–0.1 to 11.3)*	0.05	3.6%	*(–3.5 to 11.3)*	0.33	0.40
PreHD-B	–1.10	*(–1.62 to –0.59)*	<0.001	7.3%	*(0.2 to 14.9)*	0.04	–0.9%	*(–9.4 to 8.4)*	0.84	0.002
HD1	–1.38	*(–1.83 to –0.93)*	<0.001	24.2%	*(15.8 to 33.1)*	<0.001	10.5%	*(2.3 to 19.3)*	0.01	<0.001
HD2	–2.01	*(–2.56 to –1.45)*	<0.001	35.1%	*(23.4 to 48.0)*	<0.001	17.4%	*(5.2 to 31.0)*	0.004	<0.001

[a]All results are adjusted for age, sex, educational level and study site; [b]Age, expected years to onset and disease duration as at baseline; [c]Education level as a proxy for Intelligence Quotient, as based on the ISCED education classification system; [d]For ease of interpretation, the log RT values were back-transformed to the original millisecond scale and these results were reported; [e]The interaction represents the difference in estimated RTs for correct and incorrect responses for each HD subgroup compared with the same difference in Controls; [f]The difference in estimated RT for correct and incorrect responses is larger in the HD subgroup than the difference in controls. In all other cases the difference in RT for correct and incorrect responses is smaller in the HD subgroup than the difference in controls. [g]Longitudinal outcomes for set size 5 is reported elsewhere; see Tabrizi et al. [3].

results indicating lower working memory capacity at all levels of task difficulty.

Response time results indicated that premanifest and early stage HD participants were slower than controls when responding correctly to the task trials. This is particularly relevant as the premanifest gene-carrier group were restricted to those who were free of clinically evident motor signs. Given the lack of significant motor signs in this group, we believe that the slower response times observed may indicate slowed cognition or information processing rather than slowed motor processing. Our finding is consistent with previous findings of psychomotor slowing in premanifest groups [8, 22]. We also note that the working memory task included a long response time frame (8 seconds), to allow participants, even those with early HD who have proven motor deficits, to respond to the trials within the time frame. The task design therefore eliminated any potential differences in response times being attributed to missing data in the early HD group. Not surprisingly, the differences between response times for correct and incorrect trials (at each set size) were greatest in the control group and the PreHD-A group, whereas with greater levels of the

disease, this differentiation in response times broke down.

A key strength of the current paper is that by examining speed and accuracy together, we can further understand how slowing and accuracy are related within a working memory task. In previous studies however, psychomotor speed and working memory have been examined in separate tasks. In premanifest gene-carriers and controls, we found that response times and working memory capacity were not significantly related to each other. More specifically, we did not find evidence for a speed-accuracy trade-off in any participant group. A speed-accuracy trade-off would have been apparent if faster responders showed less accuracy than slower responders [51]. On the contrary, we found evidence that in early stage HD the opposite is true, such that slower responses were associated with less accurate performances and thus lower visual working memory capacity.

Similar to longitudinal (12-month) results previously reported [3], our findings suggest that poor visuospatial working memory in early HD is characterised by both slower responses times and lower accuracy. This kind of relationship or co-occurrence of slow speed and low accuracy could be termed the "worse-worse phenomenon". That is, although the premanifest gene-carriers demonstrated significantly slower response times as well as a poorer working memory capacity when compared to controls, there was no statistical evidence of a relationship between the two. Because motor slowing can be present at the same time as poor cognitive performance in the absence of a relationship between the two, as is seen in the premanifest gene-carriers, the presence of motor slowing does not directly implicate it as a primary cause of poorer cognitive performance. Therefore, the presence of a "worse-worse phenomenon" indicates that poor cognitive performance cannot be explained by slow response times only. These impairments are in line with the neuropathology of HD whereby regions implicated in normal working memory processes, that is, regions of the frontostriatal brain circuit, are also the key regions implicated in the pathology of HD which has additional implications for driving of motor responses [28–31].

A strength of the current study is that the visual working memory task used in this study included a reasonably large number of trials, thereby providing relatively robust estimates of working memory capacity across three difficulty levels. The task can be argued to assess visuospatial rather than verbal working memory because it uses a random selection of colours and location of squares between trial pairs, which makes the use of verbal encoding strategies unlikely. In addition, this design also appears to have minimal practice effects.

One limitation is that it is not possible to eliminate deficits in basic attention as a cause for poor task performance. However, the short trial duration was designed to limit the impact of short attention spans on task performance. It is also important to realise that attentional functions are interlinked with working memory, and the role of attention in cognitive processing is complex. In fact, Cowan [46] argued that working memory tasks, such as the Spot the Change task, assess the scope of attention, a key factor that limits working memory capacity. As HD progresses, there may be a decrease in the ability to adequately attend to and extract relevant information from the task at hand. Therefore, although attention span is not directly assessed by this task, attention processes play a role in the task outcome. This could be reflected in the "worse-worse phenomenon" whereby it may be more difficult for patients with HD to extract the needed information from the stimuli, as well as being slower at integrating the information from the first and second arrays.

It is important to note that this report solely addressed cross-sectional findings. Inferences about longitudinal effects cannot be made with certainty. Another consideration with regard to generalisability of our findings is that premanifest samples across studies can vary considerably, and thus the specific characteristics of the sample should be taken into account in the interpretation of the results. For example, our study, while it included premanifest subjects with relatively high disease burden, it excluded premanifest subjects with subtle motor signs by restricting the UHDRS motor score to 5 or less. Other samples, such as in PREDICT-HD, included premanifest samples regardless of motor scores. Because the presence of motor signs is more indicative of approaching disease diagnosis, it is likely that the PREDICT-HD sample is relatively closer to disease diagnosis on average than our TRACK-HD sample. The decision to exclude premanifest subjects with subtle motor signs from the TRACK-HD sample was made to allow for the investigation of cognitive impairments in the relative absence of motor signs in the premanifest period.

In summary, we conclude that visual working memory impairment can be detected in both premanifest gene-carriers and early stage HD patients using the Spot the Change task. In early stage HD, we observed a "worse-worse phenomenon" whereby lower accuracy was associated with slower responses, the opposite

of a speed-accuracy trade-off. Our findings, together with other reports in the literature, suggest that working memory tasks are useful markers of cognitive deterioration in HD. Such deterioration may be most sensitively detected in early HD, especially stage 2, using moderate to higher working memory loads along with measures of working memory capacity and response times for correct trials. This sort of cognitive task may be applicable in short term clinical trials (of 12 or more month duration) of disease modifying or symptomatic treatments for participants in stage 2 HD. Future examination of longitudinal effects in the most difficult condition, set size 7, once such data become available from the TRACK-HD study, may reveal added task sensitivity for premanifest gene-carriers or stage 1 HD.

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