Huntington's disease : functional and structural biomarkers

Dumas, E.M.

Chapter 3

Working memory impairment in premanifest gene carriers and early Huntington's disease

Eve M Dumas[1], Miranda J Say[2], Rebecca Jones[3], Ellen P Hart[1], Simon JA van den Bogaard[1], Sarah Queller[4], Damian Justo[5], Allison J Coleman[6], Rachelle C dar Santos[6], Alexandra Durr[5], Blair R Leavitt[6], Sarah J Tabrizi[2], Raymund AC Roos[1], Julie C Stout[7], the TRACK-HD Investigators

1.Department of Neurology, Leiden University Medical Centre, Leiden, The Netherlands
2. UCL Institute of Neurology, University College London, UK
3. Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, UK
4. Queller Consulting, Dunedin, FL, USA
5. Department of Genetics and Cytogenetics, Paris, France
6. Department of Medical Genetics, University of British Columbia,Vancouver, Canada
7. School of Psychology and Psychiatry, Monash University, Australia

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Abstract

Objective

Working memory deficits have been found in Huntington's disease (HD) and in a small group of premanifest HD gene carriers. However, the nature and extent of these deficits are not known. We aimed to determine, in a large cross-sectional and 12-month longitudinal study, the degree of visuospatial working memory dysfunction across multiple disease stages including both premanifest and early HD. We also examined the relationship between visuospatial working memory and motor dysfunction.

Method

We examined 363 participants from the TRACK-HD study, including 62 premanifest gene carriers far from estimated disease onset (preHD-A), 58 premanifest gene carriers close to disease onset (preHD-B), 77 stage 1 HD patients (HD1), 44 stage 2 HD patients (HD2), and 122 healthy controls. For the visuospatial working memory test, participants performed 64 simple and moderately difficult trials at baseline, and 64 moderate and difficult trials after 12 months.

Results

Cross-sectionally, differences in visuospatial working memory capacity were seen in PreHD-B and in the two HD groups when compared to the controls. Longitudinally, only patients in HD stage 2 showed a reduction of visuospatial working memory capacity. Speed and accuracy were positively correlated, but only in the HD groups.

Conclusions

Impairment in visuospatial working memory is detectable cross-sectionally in both premanifest and manifest stages of HD, but declines in visuospatial working memory at 12 months were only significant in HD stage 2. Furthermore, in manifest HD there is evidence for a "worse-worse phenomenon", whereby reductions were present in both motor speed and accuracy.

Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease, which is characterised by progressive motor, psychiatric and cognitive symptoms and signs. The mean age of disease diagnosis is between 35 and 45 years. 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 signs are referred to as premanifest gene carriers. Many studies investigating cognition in HD have demonstrated progressive cognitive decline resulting in dementia[1;2]. Cognitive decline is also detectable in the premanifest gene carriers across a number of domains, including executive functions, memory, emotion recognition and psychomotor functions[3-5].

Working memory is a topic of recent attention as a possible marker for disease state in HD[6;7]. 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[8]. Poorer 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[6;9;10]. Longitudinally, visual working memory span was found to decline over a period of 3.6 years in 22 patients with HD[11]. Verbal working memory has also been found to be impaired cross-sectionally in HD[10;12].

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[13-19]. With regard to working memory, the evidence in premanifest HD is unclear. Some studies have reported a decline in both verbal and visual working memory[18;20]. However, others have suggested that premanifest HD do not differ from controls in either visual or verbal working memory[14;21]. Limited longitudinal evidence is available regarding working memory in premanifest HD. However, in one study of 12 premanifest gene carriers who were tested with an extensive neuropsychological battery 3 times over a period of 2.5 years, it was suggested that working memory, in particular visuospatial working memory, may be among the first cognitive functions to show decline in the premanifest phase[7].

Working memory is implemented in complex brain networks which integrate signals received by the parietal cortex, and then project these integrated signals onto the frontostriatal brain circuits which subsequently drive motor responses[22-24]. In healthy adults, evidence from functional magnetic resonance imaging (fMRI) demonstrates the involvement of the parietal cortex in working memory. For example, short-term memory

capacity is correlated with parietal cortex blood oxygen level dependent (BOLD) activity levels[25;26]. The underlying brain regions associated with working memory are also among the primary regions implicated in the cognitive dysfunction observed in HD, namely the caudate nucleus and putamen, which lie within the frontostriatal brain circuits[12;27-30]. The brain regions which are involved in working memory overlap considerably with those regions shown to be affected structurally and functionally in both premanifest and diagnosed HD[31-33]. Measures of brain functioning during performance of working memory tasks, such as fMRI or electroencephalography (EEG), have shown that patterns of the underlying brain processes are different in premanifest gene carriers than those of controls, even in the absence of differences in working memory task performance[12;34;35]. Brain atrophy develops prior to disease diagnosis in these premanifest gene carriers, and progresses during the disease course, with the most profound and earliest changes found in the deep grey matter structures such as the caudate nucleus and putamen[31;32;36;37]. The integrity of the white matter is also affected in HD[38;39]. Given that both brain atrophy and decline in objectively assessed clinical measures have been observed more than ten years before estimated disease onset[13;15;31;37], it can be expected that deficiencies in visual working memory would develop as these brain regions deteriorate.

Motor functioning overlaps with cognitive functioning, in that both are implemented 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[15;41-43]. 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 disentangling the motor and cognitive roles 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 be less accurate due to being less careful or cautious. We hypothesized 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.

The aim of this study was to determine, using a large cross-sectional study, the degree of visuospatial working memory dysfunction across multiple disease stages including both premanifest gene carriers, and those in early stage HD. Furthermore, we wanted to examine visuospatial working memory function in HD across different levels of task complexity. We expected to find evidence of visuospatial working memory decline in early HD and also in the premanifest phase, especially given the progressively widespread grey and white matter brain changes known to occur in HD. We also 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 premanifest HD.

Methods

Participants

Three hundred and sixty-six subjects were studied as part of the TRACK-HD longitudinal observational study. 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 ≤ 5 points on the Unified Huntington Disease Rating Scale (UHDRS), and if they had Disease Burden Scores of at least 250[44]. 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[45]. Then, using a median split (10.8 years to expected onset) we divided the group into 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 patients in HD stage 1 (HD1, TFC scores 11-13) and HD stage 2 (HD2, TFC scores of 7-10) groups. Participants were studied annually, and in the current report we include baseline cross-sectional data on a visual working memory task, the *Spot the Change task* (SPOT), as well as data from the first longitudinal (12-month) visit. For information on the full cognitive assessment battery, additional examinations and detailed inclusion criteria see Tabrizi *et al.* (2009)[5].

Spot the change task

The Spot the Change task (SPOT) was based on the previously described 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), followed by a blank display (1000 ms), and then second array of coloured squares in which one of the squares had been encircled. The position of the squares was unchanged between the two presentations. Participants were then 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" could be given using the thumb of the dominant hand or "different" using the non-dominant thumb. The mouse platform included labels for the "same" and "different" responses to remind subjects which thumb corresponded to which response. Answers could be given 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. Three levels of difficulty, based on the number of coloured squares contained in the array, were used. Specifically, at baseline, the easiest level included three coloured squares (set size 3) and the harder level included five coloured squares (set size 5). At the 12-month visit, set sizes 5 and 7 were used. The easiest level, set size 3, showed a ceiling effect at baseline and was dropped from the test battery and replaced by set size 7 for the 12-month visit. This design yielded cross-sectional data on set sizes 3, 5 and 7, and longitudinal data at 12 months for set size 5. Thirty-two trials of each set size were randomly mixed, yielding a total of 64 trials at each visit. Both 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 both visits and study groups (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 (2001), computed as $k = \text{set size } \underline{n}$ ([number correct hits/number of trials] + [number correct rejections/number of trials] -1)[46]. A *k* or working memory capacity value close to the set size (e.g., 3, 5 or 7) indicates good working memory capacity, whereas working memory capacities close to or less than zero represent performances closer to chance.

Of subjects that attended the visits, only a small number of participants failed to complete the SPOT, which was nearly always due to time constraints. The SPOT was completed at the baseline visit, the 12-month visit, or at both visits by a total of 363/366 (99%) of the participants (with 1 control and 2 HD2 participants not completing the SPOT at any of the visits and were thus excluded from the analysis). The baseline visit had a total of 355 of 366 who completed the task (97%), yielding missing data for 3 controls, 5 HD1, and 3 HD2.

Three hundred and twenty five of 355 (92%) of baseline visit participants returned for the 12-month visit, with an additional 8 completing the task who did not do so at baseline. Therefore, 333 out of 366 (91%) completed the task during the 12-month visit, yielding missing data for 9 control, 1 PreA, 5 PreB, 6 HD1 and 12 HD2 during this visit.

Statistical analysis

All working memory capacity (*k*) data were analysed in a single regression model incorporating data from all levels of difficulty and both visits. Working memory capacity, *k*, was the outcome variable. The main predictors were group (controls, PreHD-A, PreHD-B, HD1 and HD2) and set size at each visit (set size 3 and 5 at visit 1; set size 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 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 the baseline visit; set sizes 5 and 7 at the 12-month).

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. Longitudinal comparisons of each gene carrier group for their set size 5 performance at the second visit (versus their performance at the baseline visit) were compared to that of controls at their 12-month visit (versus their baseline visit).

Finally, to examine the direct relationship between accuracy and RT, we computed separate linear regression models for each set size with RT as the outcome measure. For this analysis, *k* and group (controls, PreHD-A, PreHD-B, HD1 and HD2) were the main predictors. Again, age, gender, education level and study site were covariates. A group versus *k* interaction was included to allow 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) in the five groups, including both cross-sectional and longitudinal results. We then present RT findings per set size. Finally, we describe the relationship between RT and accuracy to further characterize the relationship of visual working memory to premanifest and early stage HD. The participant characteristics at baseline are shown in table 1.

Table 1 Participant characteristics at baseline

		Controls	PreHD-A	PreHD-B	HD1	HD2
Number of participants		122	62	58	77	44
Female/male		68 / 54	33 / 29	33 / 25	46 / 31	19 / 25
Age[a]	mean (SD)	46.2(10.1)	41.1 (8.6)	40.6 (9.2)	47.2 (10.3)	51.0 (8.6)
Education level[b]	mean (SD)	4.0 (1.3)	4.1 (1.1)	3.8 (1.3)	3.8 (1.3)	3.3 (1.4)
CAG repeat length	mean (SD)	-	42.1 (1.8)	44.2 (2.5)	43.8 (3.3)	43.5 (2.4)
Expected years to onset[a]	mean (SD)	-	14 (3.1)	9 (1.3)	-	-
Disease duration[a]	mean (SD)		-	-	5 (5.8)	8 (4.5)
Intervisit interval (months)	mean (SD)	11.6 (0.8)	11.5 (0.6)	11.5 (0.9)	11.6 (1.0)	11.6 (0.6)

[a]: Age, expected years to onset and disease duration as at baseline; [b]: Education level as a proxy for Intelligence Quotient, as based on the ISCED education classification system

Working memory capacity (*k*) was significantly lower for the PreHD-B, HD1 and HD2 groups at each visit and for each set size (3, 5 and 7) compared to healthy controls (Table 2 and Figure 1). PreHD-A did not show difference to controls at either visit for any set size. Set size 3 (assessed at the first visit only) demonstrated a ceiling effect in controls and both premanifest groups, but this ceiling effect was not apparent for set size 5 and 7. The 12-month longitudinal effects for set size 5, which was the only set size performed across both visits, indicated that for the HD2 group, *k* decreased by nearly half an item compared to controls over the same period (-0.46 decline in *k*, $p = 0.045$; 95% confidence interval: -0.01 *k* to -0.92 *k*). No other group showed significant decline in performance after 12 months.

Table 2. Adjusted differencesa in working memory capacity and response time for set sizes 3 and 5 at year 1 and set sizes 5 and 7 at year 2 for HD gene-carriers compared to controls

	Working memory capacity (k)			Response time (% increase)[b]						
				Correct			Incorrect			Interaction[(c)]
	Est.	95%CI	*p*	Est.	95% CI	*p*	Est.	95% CI	*p*	*p*
Year 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[(d)]
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
Year 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[(d)]
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
Year 2 – Set Size 5										
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[(d)]
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
Year 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]: For ease of interpretation, the log RT values were back-transformed to the original millisecond scale and these results are reported; [c]: The interaction represents the difference in estimated RTs for Correct and Incorrect responses for each HD subgroup compared with the same difference in Controls; [d]: 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.

The RTs in the easiest condition, set size 3, were longer in the PreHD-B, HD1 and HD2 than in controls when answering correctly, despite the ceiling effect. For set size 3 incorrect responses, only the HD2 group was significantly slower. At baseline for set size 5 (the moderately difficult trials), correct responses were slower in the PreHD-B, HD1 and HD2 than controls. At the 12-month time point, only HD1 and HD2 were slower at answering correctly than controls. Incorrect responses showed similar sensitivity. Specifically, at baseline, only the HD2 group provided slower incorrect responses compared to controls, and at 12 months, PreHD-A, HD1 and HD2 groups provided slower incorrect responses as compared to controls. In the most challenging condition, set size 7 trials, all four 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.

The relationship between motor performance and working memory capacity (*k*) was examined using only three groups to increase power, including controls, a premanifest group (PreHD-A and PreHD-B combined) and an early HD group (HD1 and HD2 combined). Across all three groups the results showed a significant overall interaction effect between trial accuracy and RT, thereby indicating that response times differed for correct as compared to incorrect responses. This is depicted in Figure 1, which shows that RTs for correct and incorrect responses converge with increasing severity of disease stage as the difficulty of the task increases. 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 speed was related to lower levels of accuracy in the manifest HD group for all set sizes. Specifically, longer RTs were associated with less accurate responses at baseline for set sizes 3 and 5, and at 12 months for set sizes 5 and 7 (all *p values* < 0.001; see Figure 1).

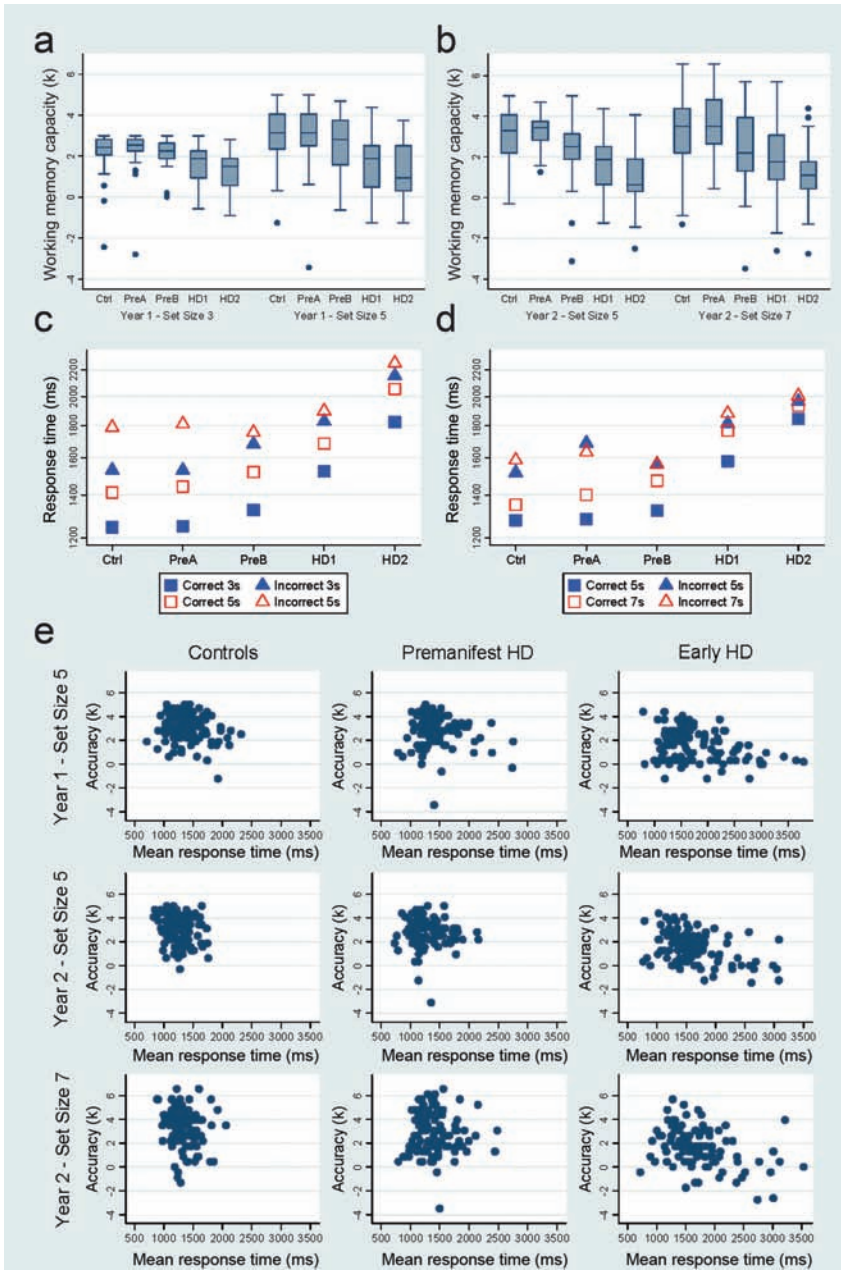

Figure 1. Ctrl = healthy controls, PreA = Premanifest gene carriers far from expected disease onset, PreB = Premanifest gene carriers close to expected disease onset, HD1 = Patients in stage 1 of the disease, H2 = patients in stage 2 of the disease, Year 1 = baseline visit, Year 2 = 12-month visit.
(a) Working memory capacity for set sizes 3 and 5 at Year 1 (b) and set sizes 5 and 7 at Year 2 for HD gene-carriers and healthy controls. (c)Response time for set sizes 3 and 5 at Year 1 (d) and set sizes 5 and 7 at Year 2. (e) Speed vs. accuracy for set sizes 5 and 7 in controls, premanifest gene carriers (pre HD) and patients (set size 3 not shown due to ceiling effect in controls and premanifest gene carriers)

Discussion

This study's main findings were that cross-sectionally, visuospatial working memory capacity is lower in both premanifest HD gene carriers who are within a decade of disease onset and in early HD patients. Secondly, over a period of one year, manifest HD patients show longitudinal decline in working memory capacity. Finally, in manifest HD, despite observing both working memory decline and slower response times, the relationship between motor response speed and accuracy was not a speed-accuracy trade-off, but rather we observed that longer response times corresponded to poorer performance.

From the cross-sectional 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. All groups responded very similarly to the moderately difficult trials at 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[50;51], and extends these findings to premanifest HD. Furthermore, despite the report by Lemiere *et al*. (2004) of a longitudinal decline in general working memory over two and a half years in pre manifest HD[7], we did not find a decline in visual working memory in premanifest HD in our 12-month follow up. Our results add to current literature in that we report, for what we believe is the first time, that decline in visuospatial working memory can be observed over a period of just 12 months in patients with stage 2 HD. We did not find a change over 12-month in premanifest gene carriers or patients at stage 1 of the disease, which could be related to a slower progression of cognitive changes at these stages of the disease. Furthermore, the task used in the current study taxed various levels of working memory capacity and our results demonstrate lower working memory capacity at all complexity levels of the task.

Response time results indicated that premanifest and diagnosed participants were slower than controls at responding to the task correctly. This is particularly relevant as the premanifest gene carriers were restricted to only those who were free of clinically evident motor signs. Given the lack of significant motor signs in this group, we believe that the slowing observed may indicate slowed cognition or information processing rather than evidence of slowed motor processing. Our finding is consistent with previous findings of psychomotor slowing in premanifest groups[15;41]. 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 time being attributed to missing data in the manifest group.

A key strength of the current paper is that in combining assessment of the response speed and accuracy, we can examine how slowing and accuracy are related within a working memory task, whereas in previous studies, 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 generally less accuracy than slower responders[52]. On the contrary, we found evidence that in manifest HD the opposite is true, such that slower responses were associated with less accurate performances and thus lower visual working memory capacity.

Our findings show that declines in visuospatial working memory in early HD are accompanied by both slower speed of responses and lower accuracy. This kind of relationship between speed and accuracy, can be described as a "worse-worse phenomenon", and cannot be explained as an epiphenomenon of HD. An epiphenomenon describes a relationship between two deficits in a disease that occur simultaneously but are in fact not related or caused by each other; however, because they occur together they seem related. The premanifest HD data from this study discount an epiphenomenon as the explanation because although the premanifest gene carriers demonstrated significantly slower response times as well as a poorer working memory capacity, there was no statistical evidence of a relationship between the two. Additionally, 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 responses times only.

The visual working memory task applied 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. 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 (2001) argue that working memory tasks, such

as Spot the Change task, assess the scope of attention, a key factor that limits working memory capacity[46]. 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.

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 the early stages of HD we observed a "worse-worse phenomenon" whereby lower accuracy was associated with slower responses; the opposite of a speed-accuracy trade-off. Importantly, the longitudinal results demonstrated that visual working memory task shows detectable decline across 12 months in stage 2 HD. 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 in 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 trials (of 12 or more month duration) of disease modifying or symptomatic treatments for participants in HD stage 2. 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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