

Visuomotor integration deficits precede clinical onset in Huntington's disease

Miranda J. Say^{a,b}, Rebecca Jones^c, Rachael I. Scahill^a, Eve M. Dumas^d, Allison Coleman^e,
Rachelle C. Dar Santos^e, Damian Justo^f, J. Colin Campbell^g, Sarah Queller^h, E. Arthur Shores^b,
Sarah J. Tabrizi^a, Julie C. Stout^{g,*}, the TRACK-HD Investigators

^a UCL Institute of Neurology, University College London, Queen Square, London, WC1N 3BG, UK

^b Psychology Department, Macquarie University, New South Wales, 2109, Australia

^c London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, UK

^d Department of Neurology, Leiden University Medical Centre, Albinusdreef 2, 2333 ZA Leiden, The Netherlands

^e Department of Medical Genetics, University of British Columbia, Vancouver, BC V6T 2B5, Canada

^f Department of Genetics and Cytogenetics, and INSERM UMR S 679, APHP Hôpital de la Salpêtrière, 75013 Paris, France

^g School of Psychology and Psychiatry, Monash University, Clayton Campus, Victoria, 3800, Australia

^h Queller Consulting, 598 Bella Loop, Dunedin, FL, 34698 USA

ARTICLE INFO

Article history:

Received 11 August 2010

Received in revised form 9 November 2010

Accepted 12 November 2010

Available online 20 November 2010

Keywords:

Huntington disease
Visuomotor integration
Premanifest
Volumetric MRI
Visuospatial function
Motor coordination

ABSTRACT

Objectives: Visuomotor integration deficits have been documented in Huntington disease (HD), with disproportionately more impairment when direct visual feedback is unavailable. Visuomotor integration under direct and indirect visual feedback conditions has not been investigated in the stage before clinical onset ('premanifest'). However, given evidence of posterior cortical atrophy in premanifest HD, we predicted visuomotor integration would be adversely affected, with greater impairment under conditions of indirect visual feedback.

Methods: 239 subjects with the HD CAG expansion, ranging from more than a decade before predicted clinical onset until early stage disease, and 122 controls, completed a circle-tracing task, which included both direct and indirect visual feedback conditions. Measures included accuracy, speed, and speed of error detection and correction. Using brain images acquired with 3T magnetic resonance imaging (MRI), we generated grey and white matter volumes with voxel-based morphometry, and analyzed correlations with circle-tracing performance.

Results: Compared with controls, early HD was associated with lower accuracy and slower performance in both circle-tracing conditions. Premanifest HD was associated with lower accuracy in both conditions and fewer rotations in the direct condition. Comparing performance in the indirect condition with the direct condition, HD gene expansion-carriers exhibited a disproportionate increase in errors relative to controls. Premanifest and early HD groups required longer to detect and correct errors, especially in the indirect condition. Slower performance in the indirect condition was associated with lower grey matter volumes in the left somatosensory cortex in VBM analyses.

Conclusions: Visuomotor integration deficits are evident many years before the clinical onset of HD, with deficits in speed, accuracy, and speed of error detection and correction. The visuomotor transformation demands of the indirect condition result in a disproportionate decrease in accuracy in the HD groups. Slower performance under indirect visual feedback was associated with atrophy of the left-hemisphere somatosensory cortex, which may reflect the proprioceptive demands of the task.

© 2010 Elsevier Ltd. All rights reserved.

1. Introduction

Huntington disease (HD) is an autosomal dominant inherited neurodegenerative condition characterized by progressive involuntary and voluntary motor dysfunction and cognitive deterioration. The voluntary motor disorder presents as slowed

movements (Hefter, Homberg, Lange, & Freund, 1987) that are irregular in velocity, force and timing (Quinn, Reilmann, Marder, & Gordon, 2001). Neuroimaging and neuropathological studies have historically focused on striatal atrophy, which occurs early in the disease process and is a neuropathological hallmark of HD. However, recent neuroimaging studies have documented prominent progressive cortical thinning in parietal and occipital cortices, even in the years preceding motor onset (Rosas et al., 2002, 2005). Given this posterior cortical involvement together with striatal atrophy, HD patients likely show deficits in activities that have visual, spatial and motor demands. Such deficits are important to under-

* Corresponding author. Tel.: +61 3 9905 3987; fax: +61 3 9905 3948.
E-mail addresses: julie.stout@monash.edu.au, julie.stout@monash.edu (J.C. Stout).

stand because of their functional implications. For example, driving requires an integration of visual, motor and spatial demands.

Several studies in manifest HD using small subject samples (<20) have demonstrated deficits in visuomotor integration in laboratory-based tasks (Boulet et al., 2005; Georgiou, Bradshaw, Phillips, Chiu, & Bradshaw, 1995; Lemay, Chouinard, Richer, & Lesperance, 2008; Lemay, Fimbel, Beuter, Chouinard, & Richer, 2005). In addition, motor control during visually guided rapid arm movements has been shown to be relatively jerky in premanifest and manifest HD patients (Smith, Brandt, & Shadmehr, 2000). Given these findings of problems of visuomotor integration deficits, and neuroimaging findings in premanifest and manifest HD document atrophy in brain regions strongly associated with visual, spatial and motor processes, a primary goal of the current study was to extend these findings to a large, stratified sample that would make it possible to differentiate whether visuomotor integration deficits are present more than 10 years prior to estimated onset in the premanifest period, and whether these findings could be consistently observed across both Stage 1 and Stage 2 (early) HD.

A seminal study of visuomotor integration in HD by Lemay et al. (2005) examined the effects of varied levels of visual feedback on accuracy and efficiency in a visuomotor integration task. Thirteen subjects with manifest HD and a comparison group of control subjects were asked to trace a circle on a computerized touchscreen laptop placed horizontally in front of them. One condition provided *direct* visual feedback during tracing, which allowed the subject to view their hand and the resulting trace path directly on the screen on which they traced. In the other condition, the subject's tracing hand was obscured. Instead the subject was provided with a second computer monitor displaying their tracing path in a vertical position in front of them. This latter *indirect* visual feedback condition was more challenging in that it required visual information presented in one plane (vertical) and proprioceptive cues in a another plane (horizontal) to be transformed into a common frame of reference to produce accurate motor output (Lemay et al., 2005).

Lemay et al. (2005) found that HD patients performed more slowly and made more errors than controls in both direct and indirect circle-tracing conditions. Unsurprisingly, controls performed more poorly in the indirect than the direct condition in terms of speed and accuracy. HD patients, compared with controls, displayed a disproportionate reduction in accuracy and speed of tracing when contrasting performance in the indirect with the direct condition. The HD group also spent longer for detecting and correcting errors in both conditions, as indicated by longer trace durations away from and towards the target, respectively. Interestingly, Lemay et al. found that HD was associated with a more pronounced delay in error correction than error detection in the indirect condition. This is somewhat surprising given the role of the striatum in error detection during motor actions (Falkenstein et al., 2001). Furthermore, the striatum has been linked to the selec-

tion of motor actions in response to environmental cues (Marsden & Obeso, 1994), which would be more consistent with greater delays in error detection than in error correction. In addition, dysmetric overshooting has been observed in HD patients (Carella et al., 2003), which could contribute to greater error detection delays.

This study extends the work of Lemay et al. (2005) by examining direct and indirect visuomotor integration in a large cohort of premanifest and manifest HD subjects. To our knowledge, no studies thus far have contrasted direct and indirect visual feedback on visuomotor integration in premanifest HD. Consistent with Lemay et al., we predicted that HD would be associated with more errors and slowed performance in both the direct and indirect conditions. We also predicted that deficits would be present in premanifest HD. Furthermore, owing to the relatively greater visuomotor transformation demands in the indirect compared with the direct condition, we predicted that the indirect condition would be more sensitive in revealing deficits in the premanifest period. Importantly, given the somewhat surprising findings of greater delays in error correction than in error detection reported by Lemay et al., we re-examined error types to see whether this differential error effect could be replicated in a larger sample. Finally, given the findings in separate studies suggesting, on the one hand, posterior cortical changes and, on the other hand, deficits in visuomotor integration in HD, we tested the possibility that these findings could be related by examining the relationships between regional grey and white matter volumes and circle-tracing performance in premanifest and manifest HD.

2. Methods

2.1. Participants

Three hundred and sixty-one subjects from the TRACK-HD study (Tabrizi et al., 2009) participated at four study sites: London, Leiden, Paris and Vancouver. All at-risk individuals had undergone genetic testing prior to recruitment. Those with genetically confirmed CAG repeats in the normal range were included in the control group, along with partners of HD gene expansion-carriers. As part of the study, all HD gene expansion-carriers were re-sized for CAG repeat length at Bioprep, Milan. Subjects were included in the premanifest groups if their burden of pathology score was greater than 250 (age \times [CAG – 35.5] (Penney, Vonsattel, MacDonald, Gusella, & Myers, 1997), but they had no substantial motor signs, as measured by the Unified Huntington's Disease Rating Scale-99 (UHDRS-99: total motor score \leq 5) (Huntington Study Group, 1999). The premanifest sample was then split at the median time to estimated onset of motor symptoms (10.8 years), computed as per Langbehn, Brinkman, Falush, Paulsen, and Hayden (2004), into furthest from estimated onset 'PreHD-A' and closer to estimated onset 'PreHD-B'. For those subjects with manifest HD, we classified them as HD Stage 1 'HD1' and HD Stage 2 'HD2' according to Shoulson and Fahn (1979) criteria. We attempted to match the ages of the HD-gene expanded groups with the control group. However, the premanifest group was younger than the early HD group, which is expected given the progressive nature of HD (see demographics in Table 1). Other inclusion criteria were: being aged between 18 and 65 years; suitability for MRI; having no concomitant major psychiatric, neurological or medical illness, current illicit drug use or participation in a drug trial; and no history of significant head injury. Further details of subgroup selection are outlined in Tabrizi et al. (2009). Local ethics committees at each site approved the study. Each subject gave written informed consent.

Table 1

Subject demographics, CAG repeat length, disease burden score, predicted years to onset and clinical variables by group.

	Controls <i>n</i> = 122	PreHD-A <i>n</i> = 62	PreHD-B <i>n</i> = 57	HD1 <i>n</i> = 75	HD2 <i>n</i> = 45
Sex (F:M)	67:55	33:29	33:24	45:30	21:24
Age in years ^a	46.0 (10.2)	41.1 (8.6)	40.6 (9.3)	47.6 (10.0)	51.2 (8.6)
Educational level ^{a,b}	4.0 (1.3)	4.1 (1.1)	3.8 (1.3)	3.8 (1.3)	3.2 (1.4)
CAG repeat length ^a	–	42.1 (1.8)	44.2 (2.5)	43.6 (2.8)	43.5 (2.4)
Disease burden score ^a	–	259.1 (30.1)	332.3 (29.7)	362.3 (72.0)	396.4 (67.8)
Predicted years to onset ^{a,c}	–	14.1 (3.1)	8.7 (1.3)	–	–
UHDRS total motor score ^a	1.5 (1.7)	2.2 (1.4)	2.8 (1.8)	19.4 (9.2)	30.1 (9.3)
UHDRS total functional capacity ^a	13.0 (0.1)	12.9 (0.4)	12.8 (0.7)	12.3 (0.9)	8.6 (1.1)

^a All data are represented as *M* (*SD*).

^b Education level based on the ISCED education classification system (UNESCO, 1997).

^c Langbehn et al. (2004).

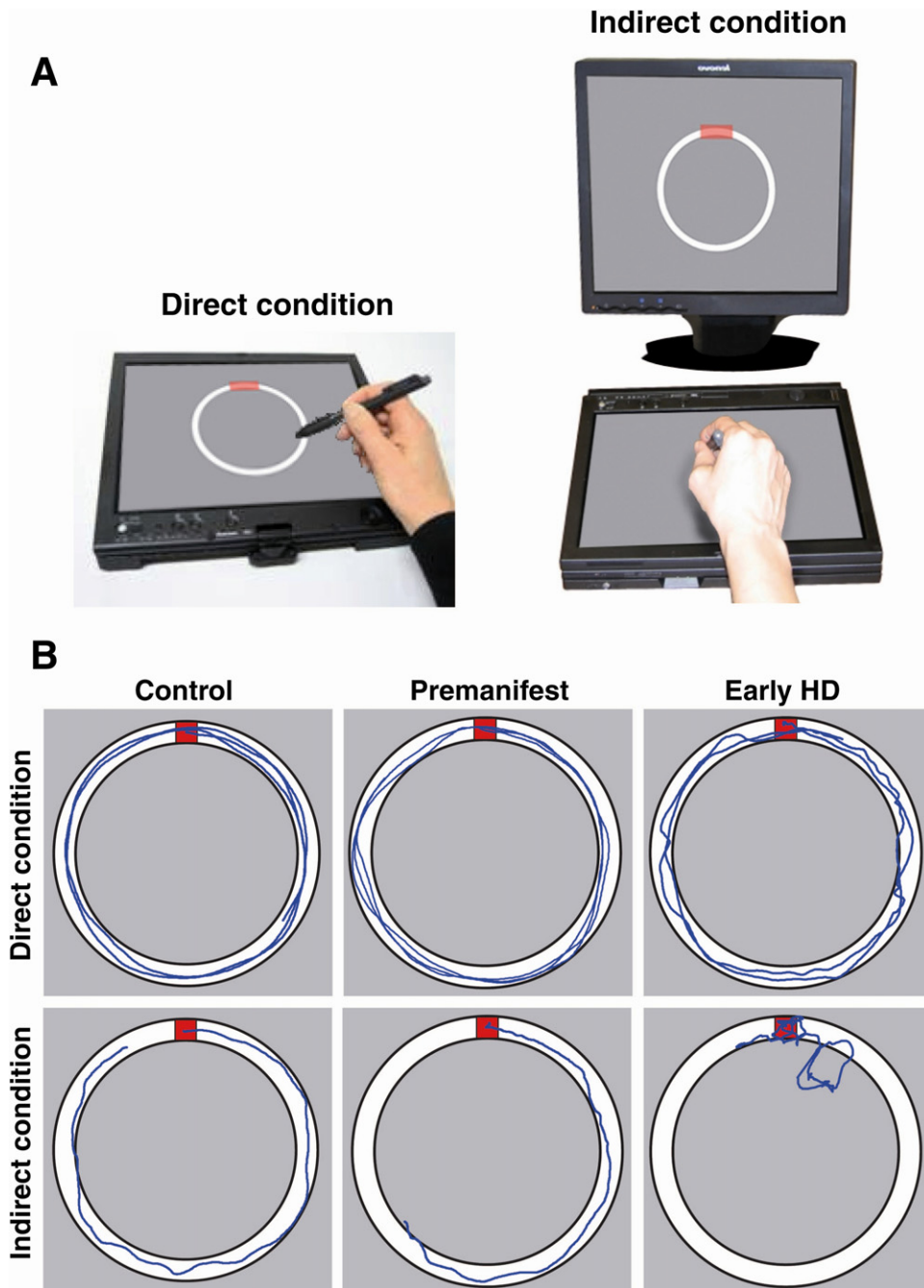


Fig. 1. Circle tracing apparatus and sample traces. (A) A right-handed subject tracing a circle on a horizontally positioned laptop for the direct condition (left top) and the indirect condition (right top) using indirect feedback projected on a second, vertically positioned monitor. Note that although not shown here, in the indirect condition the subject's hand was obscured from sight by a suspended sheet. (B) Sample performances from a control, a premanifest, and an early HD subject during the first 10 s of the first trial.

2.2. Materials and procedures

2.2.1. Circle-tracing task

Subjects completed a circle-tracing task that included both direct and indirect conditions. The task was administered on a horizontally placed Lenovo ThinkPad X61 tablet laptop, using an additional vertically placed desktop monitor for the indirect condition (see Fig. 1). For both conditions, the subject viewed a display showing a 90 mm diameter circle and 5 mm thick white annulus on a grey background. As the subject traced the circle, a thin line reflecting the trajectory of their tracing path appeared in blue on the display. For both conditions, subjects were instructed to start at the vertical apex of the circle and trace as quickly and accurately as possible in the clockwise direction without leaning their hand on the screen. In the direct condition, subjects could directly observe both their hand and the path they were tracing on the tablet screen. In the indirect condition, the subject's arm and the tablet were obscured from sight by a suspended sheet. Feedback was viewed instead on

a separate display monitor in vertical orientation about 80 cm in front of them, showing a copy of the target circle and the stylus trajectory. The approximate visual viewing angle for both the direct and indirect conditions was 55° in the horizontal axis, but on the vertical axis, it was approximately 55° in the indirect condition, but somewhat less, approximately 50° , in the direct condition due to the difference in distance from the eyes between the top of the circle, which was relatively further away than the bottom of the circle. This difference was not expected to have created additional difficulty in the direct condition. Subjects completed three 45-s trials in each condition. The order of conditions administered was counterbalanced across subjects.

Prior to the task, a practice trial was administered. Most subjects completed just one rotation for practice. If a subject appeared not to have grasped the basic task requirements (for example, tracing anti-clockwise), they were permitted to continue practicing until they appeared to comprehend the requirements of the task.

Outcome measures from the circle-tracing task included: (1) as an index of *speed*, the total number of rotations completed; and (2) as an index of *accuracy*, the number of outward errors per rotation. Errors were considered to have occurred each time the stylus was moved beyond the outer edge of the annulus for >100 ms. Additionally, we distinguished errors according to a period of error detection, defined as the average time per rotation spent tracing beyond the outer limit of the annulus *away* from the circle, and error correction, defined as the average time per rotation spent tracing beyond the outer limit of the annulus *towards* the circle. We applied a log transformation to the number of rotations, and square root transformations to all error measures to improve normalization of the data, and used the resulting transformed data in the data analyses.

2.2.2. Magnetic resonance imaging (MRI) acquisition and analysis

Subjects underwent high resolution sagittal T₁- and T₂-weighted MRI on 3-T Siemens (Siemens AG, Australia) or Phillips (Royal Philips Electronics Inc, Amsterdam) whole body scanners. T₁-weighted images were acquired using a 3D MPRAGE acquisition sequence with the following imaging parameters (Siemens/Philips): TR = 2200 ms/7.7 ms, TE = 2.2 ms/3.5 ms, FA = 10°/8°, FOV = 28 cm/24 cm, matrix size 256 × 256/224 × 224 208/164, slice thickness 1.0 mm, no slice gap.

Volumetric analyses were performed only in premanifest and HD subjects, but not in controls. Only right-handed subjects were included to avoid the possible confounding effects of hemispheric asymmetry. In total, we analyzed 179 structural MRI datasets. Voxel-based morphometric analysis was performed using statistical para-

metric mapping (SPM) version 5 (www.fil.ion.ucl.ac.uk/spm). Grey and white matter segments were generated using unified segmentation and DARTEL, after which they were modulated and smoothed with a 4 mm full width at half maximum kernel.

2.2.3. Data analyses

Separate regression models were fitted for number of rotations and number of errors per rotation. The main predictors in these two models were Group (Controls, PreHD-A, PreHD-B, HD1 and HD2), Condition (Direct and Indirect) and a Group × Condition interaction. We analyzed error detection and correction together in a third model using error time per rotation as the outcome using Group, Condition and Direction (Away and Towards) as predictors. In this third model we also specified a three-way Group × Condition × Direction interaction as well as all two-way interactions. All three models were fitted using generalized estimating equations (GEE) with a working assumption of exchangeability, and robust standard errors (Liang & Zeger, 1986). This approach allows for correlation between the repeated measures for each participant, but, unlike repeated measures analysis of variance, it places no homogeneity restrictions on the variances of each measure or on the magnitude of the correlations between pairs. GEE test statistics are referred to as chi-square distributions (rather than *F* or *t* distributions) to assess statistical significance. All analyses were adjusted for age, sex, educational level and site.

A hypothesis-free analysis was performed to explore associations between grey and white matter and the measures from the circle-tracing task. Regression analyses were performed with age, gender, study site, education, CAG, disease burden and

Table 2

Estimate values, 95% confidence intervals, and *p* values comparing HD gene expansion-carrier groups with controls on the variables: number of rotations, number of errors per rotation (square root transformed), and out error time per rotation (square root transformed).

	PreHD-A vs. controls	PreHD-B vs. controls	HD1 vs. controls	HD2 vs. controls
Number of rotations (as percentage of controls)				
Direct				
<i>M</i>	85.1	81.5	72.6	56.6
95% CI	[74.6, 97.1]	[70.6, 94.2]	[63.3, 83.2]	[48.1, 66.7]
<i>P</i>	0.017	0.006	<0.001	<0.001
Indirect				
<i>M</i>	91.6	83.1	67.3	63.5
95% CI	[76.4, 109.9]	[70.5, 97.9]	[57.4, 78.8]	[53.5, 75.3]
<i>P</i>	0.3	0.027	<0.001	<0.001
Indirect vs. Direct				
<i>M</i>	107.6	101.9	92.7	112.1
95% CI	[93.1, 124.3]	[89.0, 116.7]	[80.8, 106.4]	[97.7, 128.6]
<i>P</i>	0.3	0.8	0.3	0.1
Number of errors per rotation (square root)				
Direct				
<i>M</i>	−0.07	0.06	0.23	0.35
95% CI	[−0.13, 0.002]	[−0.01, 0.14]	[0.16, 0.30]	[0.22, 0.49]
<i>P</i>	0.057	0.09	<0.001	<0.001
Indirect				
<i>M</i>	0.17	0.31	0.64	0.92
95% CI	[0.02, 0.32]	[0.17, 0.45]	[0.47, 0.80]	[0.67, 1.16]
<i>P</i>	0.027	<0.001	<0.001	<0.001
Indirect vs. Direct ^a				
<i>M</i>	0.23	0.25	0.41	0.56
95% CI	[0.08, 0.39]	[0.11, 0.39]	[0.25, 0.58]	[0.34, 0.79]
<i>P</i>	0.003	0.001	<0.001	<0.001
Out error time per rotation (square root milliseconds)				
Direct/Away				
<i>M</i>	−0.90	0.55	2.60	4.84
95% CI	[−1.86, 0.07]	[−0.50, 1.60]	[1.50, 3.70]	[2.93, 6.75]
<i>P</i>	0.07	0.3	<0.001	<0.001
Direct/Towards				
<i>M</i>	−0.78	0.57	2.76	4.98
95% CI	[−1.72, 0.16]	[−0.45, 1.59]	[1.68, 3.85]	[3.07, 6.89]
<i>P</i>	0.1	0.3	<0.001	<0.001
Indirect/Away				
<i>M</i>	1.75	5.09	11.59	16.41
95% CI	[−0.97, 4.48]	[1.86, 8.33]	[8.20, 14.99]	[11.10, 21.71]
<i>P</i>	0.2	0.002	<0.001	<0.001
Indirect/Towards				
<i>M</i>	1.46	4.58	10.78	16.34
95% CI	[−0.98, 3.89]	[1.68, 7.49]	[7.71, 13.85]	[11.30, 21.38]
<i>P</i>	0.2	0.002	<0.001	<0.001

Note: Number of rotations was transformed to the log scale for analyses, thus, the estimated differences between HD-gene carrier groups and controls shown in this table were a result analyses on log transformed data. However, to facilitate interpretability for display of the findings in this table, the results were back transformed and expressed as a percentage of the number of rotations in controls. The number of errors per rotation and error time per rotation was transformed to square roots for analyses. Estimated differences between HD groups and controls for these outcomes are thus reported on the square root scale. If controls scored 250 on the original scale, an estimated difference of 5 relative to controls on the square root scale is equivalent to a raw score in the HD group in question of $(\sqrt{250+5})^2 = 433$ or a difference of $(\sqrt{250+5})^2 - 250 = 183$ on the original scale.

^a Increase in the number of errors per rotation (vs. controls) in the indirect condition compared to direct condition (square root).

intracranial volume as covariates. Associations between grey and white matter and circle-tracing measures were examined using statistical parametric maps, which provided information on how volume related to task performance after correction for overall disease severity and the other covariates. These results were corrected for multiple comparisons using the false discovery rate set at the default value of $q < 0.05$.

3. Results

3.1. Accuracy and speed

As expected, we found a main effect of condition showing that the indirect condition yielded slower performances (number of rotations $\chi^2(1) = 2456.21$; $p < 0.0001$) and more errors (number of outward deviations from the annulus target, $\chi^2(1) = 371.10$; $p < 0.0001$). Importantly, we also found highly significant group effects on speed (number of rotations $\chi^2(4) = 53.46$; $p < 0.0001$) and accuracy (number of errors $\chi^2(4) = 131.9$; $p < 0.0001$). Specifically, pairwise comparisons showed that each expansion-carrier group was significantly slower (i.e., completed fewer rotations) than controls in both the direct and indirect conditions, with the only exception being the PreHD-A group in the indirect condition (see Table 2). In the direct condition, PreHD-A completed 85.1%, PreHD-B completed 81.5%, HD1 completed 72.6% and HD2 completed 56.6% of the number of rotations completed by controls. In the indirect condition, PreHD-A completed 91.6%, PreHD-B 83.1%, HD1 67.3% and HD2 63.5% of the number of rotations completed by controls (see Table 2 for 95% confidence interval ranges). Pairwise comparisons also indicated that all premanifest and early HD groups made significantly more errors than controls in the indirect condition, whereas, in the direct condition, only the two manifest groups made significantly more errors than controls, and PreHD-A tended towards more accurate performance than controls ($p = 0.057$).

3.2. Visuomotor transformation

To determine whether the visuomotor transformation demands of the indirect condition led to greater impairment in pre-manifest and early HD compared to controls, we examined Group \times Condition interactions within the same models examined for the speed and accuracy results above. As predicted, the effect of increasingly severe levels of HD (i.e., PreHD-A < PreHD-B < Stage 1 < Stage 2) on number of errors was greater for the indirect condition than the direct condition as indicated by a significant Group \times Condition interaction ($\chi^2(4) = 47.75$; $p < 0.001$). There was no Group \times Condition interaction in speed as measured by the number of rotations. On average, all groups completed approximately three times as many rotations in the direct as in the indirect condition (estimate: 3.26 times; 95% CI: 3.11–3.43).

3.3. Error detection and error correction

For the direct visual feedback condition, time spent on error detection vs. error correction did not differ as a function of group, as indicated by a non-significant Direction (away from the annulus vs. towards the annulus) \times Group interaction ($\chi^2(4) = 4.56$; $p = 0.34$). Moreover, across groups the amount of time spent on error detection was comparable to that spent on error correction, as indicated by a lack of main effect of Direction ($\chi^2(1) = 2.56$; $p < 0.11$). Consistent with the findings for number of errors reported above, greater levels of disease severity were associated with longer durations of error detection and correction, as indicated by a significant main effect of Group ($\chi^2(4) = 75.48$; $p < 0.0001$).

In contrast to the direct condition, in the indirect condition across groups, subjects spent significantly more time on error detection (i.e., deviation away from the annulus) than on error cor-

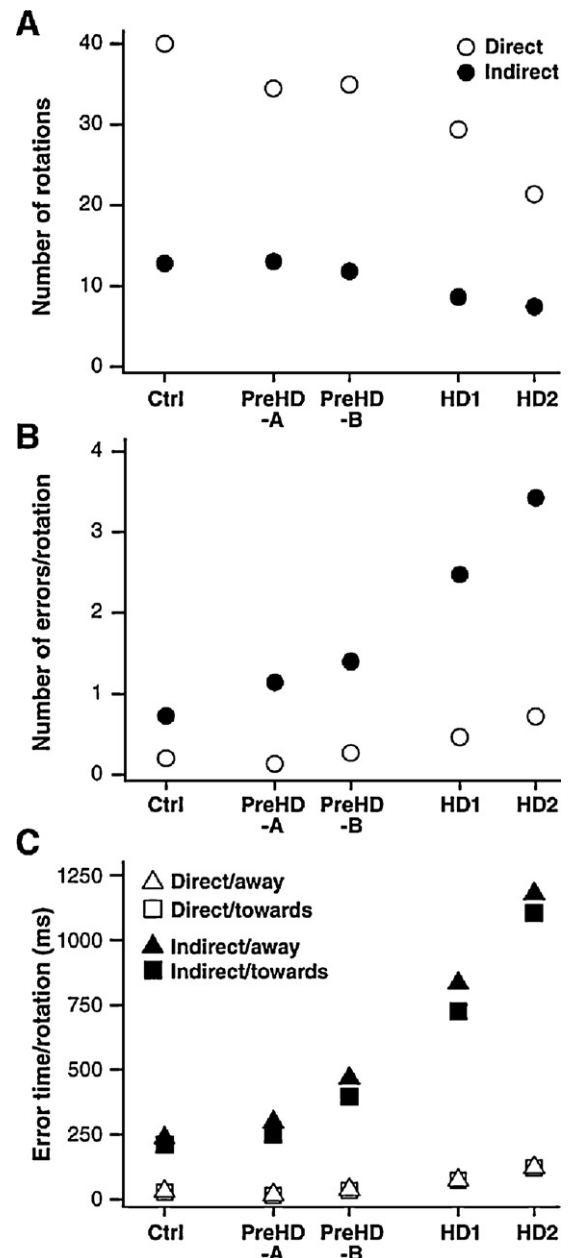


Fig. 2. A comparison of direct and indirect circle tracing task performance across groups. (A) Fewer rotations were completed on the indirect condition, completion of fewer rotations was associated with increased disease burden, and the ratio of rotations in the indirect compared with the direct condition was similar in HD groups and controls. (B) There were more errors in the indirect condition, HD groups produced more errors than controls, and the trend for more errors on the indirect than the direct condition became more pronounced in association with increased disease burden. (C) Time spent outside the annulus target split into error detection and error correction times for the direct and indirect conditions by group.

rection (i.e., tracing back towards the annulus), as indicated by a significant main effect of error direction, $\chi^2(1) = 50.09$; $p < 0.0001$. Along with this main effect of error direction, there was a significant main effect of group ($\chi^2(1) = 84.65$; $p < 0.0001$), with PreHD-B, HD1 and HD2 (but not PreHD-A) spending significantly more time on error detection and correction compared with controls. However, there was no significant interaction between error direction and group ($\chi^2(4) = 5.25$; $p < 0.26$) (see Fig. 2). Thus, in contrast to the results reported by Lemay et al. (2005), we found no preferential deficit in either error detection or correction as a function of disease status.

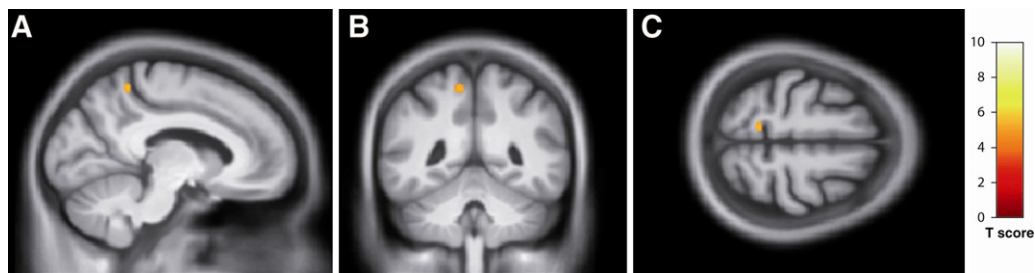


Fig. 3. Statistical parametric maps of grey matter atrophy associated with CT task performance. Panels (A) sagittal view; (B) coronal view; and (C) axial view show atrophy within the medial segment of the post-central gyrus in the left parietal lobe correlating significantly with number of rotations on the indirect condition for right-handed HD gene expansion-carriers.

Overall, error correction and detection consumed significantly more time in the indirect than in the direct condition, an effect that was increasingly pronounced across the HD groups as shown by a significant Group \times Condition interaction across both error directions ($\chi^2(4) = 44.54$; $p < 0.0001$). Taken together, the results for number of errors and for error detection and correction times suggest that the increased visuomotor transformation demands of the indirect condition have a more detrimental effect on accuracy for individuals with premanifest and early HD than the direct condition in which visuomotor transformation demands are minimal. However, there is no evidence in our data of differential effect of HD on error detection vs. correction.

3.4. Associations between circle-tracing performance and grey and white matter volumes

For the *direct* condition, we found no significant associations between either speed or accuracy measures from the circle-tracing task and the regional grey or white matter volumes at the $q < 0.05$ level. Similarly, we found no significant correlations between circle-tracing measures and regional grey and white matter volumes in the *indirect* condition, except that lower grey matter volumes in the medial post-central gyrus of the left parietal lobe (i.e., primary somatosensory cortex), were significantly correlated with slower performance (i.e., few rotations) (see Fig. 3).

4. Discussion

Our results document the presence of visuomotor integration deficits in a large cohort of premanifest and early HD CAG-expansion carriers in conditions of both direct and indirect visual feedback. As predicted, and consistent with the findings of Lemay et al. (2005), the data showed that the HD patient groups performed more slowly and less accurately than controls in both direct and indirect conditions. The current data extend these earlier findings by demonstrating the sensitivity of a circle-tracing task in *premanifest* HD. Specifically, in the direct condition, both premanifest groups, PreHD-A and PreHD-B, were slower than controls, and in the indirect condition, PreHD-B was slower than controls. Both premanifest groups were significantly less accurate than controls in the indirect condition, whereas PreHD-B performed with similar levels of accuracy to controls in the direct condition and PreHD-A showed a tendency for greater accuracy than controls. The pattern of data for the PreHD-A group in the direct condition indicates a different response style than controls, with more accurate, slower performance. Overall, these findings are noteworthy as they demonstrate visuomotor integration deficits more than a decade before estimated clinical diagnosis.

Overall, HD was associated with slowed performance in both visual feedback conditions, which most likely reflects psychomotor slowing. In contrast, accuracy was disproportionately compromised in HD groups when indirect visual cues were used, which is

suggestive of a more cognitive explanation. The reduced accuracy in the indirect condition cannot be accounted for by choreic movements given that errors did not feature prominently in the HD group in the direct condition. We believe that this increased error effect in the indirect condition may have a more neurocognitive basis given the added complexity of the indirect visual feedback condition, which necessitates greater reliance on proprioceptive feedback and on the transformation of movement trajectories across different frames of reference. The increased error effect in the indirect feedback condition may also reflect the relatively greater visuospatial, rather than motor, demands required for using indirect visual feedback to execute the tracing movement. These findings in the indirect visual feedback condition are consistent with a study by Carella et al. (2003), in which blindfolded HD patients drew a square at a similar speed as controls, but with less accuracy. The finding in our study that accuracy decreased disproportionately in the indirect condition, and that such an effect was apparent even in the PreHD-A group, suggests that tasks with high demands for visuomotor transformation and the use of proprioception may be highly sensitive to early disease processes. If these effects can be extended in a longitudinal analysis, then the indirect circle-tracing condition may be useful as a clinical marker of disease progression in premanifest HD.

Interestingly, imaging correlations revealed an association only between slower tracing in the indirect condition and lower volumes in a region of the left somatosensory cortex. The somatosensory cortex is implicated in proprioception and tactile functions (Burton & Sinclair, 2000; Nelson, Staines, & McIlroy, 2004). Thus, this structure–function correlation is consistent with the proprioceptive demands of the indirect condition and previously published findings of somatosensory cortex degeneration in HD (Rosas et al., 2005). The lack of association between speed and accuracy measures from the circle-tracing task and volumes of the visual and motor cortices may be attributable to the multifactorial demands of the circle-tracing task and/or the multiple functions of the visual and motor regions of the cortex. Alternatively, there may simply be a lack of sensitivity for relating structural imaging measures with tasks such as the circle-tracing task; volumetric MRI detects macroscopic structural change and other imaging modalities may be more sensitive to subtle early dysfunction. Nevertheless, considering the visual processing demands of circle-tracing, the data are suggestive of a functional impact of posterior cortical pathology on the clinical phenotype of HD, even in premanifest expansion-carriers, in line with imaging data of posterior pathology in this stage of the disease process (Rosas et al., 2002, 2005).

A second focus of the study was on whether HD is associated with a more pronounced delay in error correction, as suggested by Lemay et al. (2005), or error detection. In contrast with Lemay et al.'s findings and our hypothesis, we found that error detection vs. correction did not differ as a function of group for either the direct or indirect condition. Greater levels of disease severity were, however, associated with delays in both error detection and cor-

rection. In the direct condition, this effect was only detected in the manifest HD1 and HD2 groups, which spent significantly longer on both error detection and correction than controls. The effects in the indirect condition were somewhat more consistent, with longer error detection and correction in the PreHD-B, HD1 and HD2 groups. Thus, our data demonstrate delays in detection and correction in both premanifest and early HD, but no preferential deficit in either error detection or correction as a function of disease status.

There are several possible reasons for the discrepancy between our findings and those reported by Lemay et al. (2005) in error detection/correction. We do not know how comparable Lemay et al.'s manifest HD group was to our manifest group in terms of disease severity, as they did not specify the UHDRS motor or total functional capacity scores. However, because we found increased time spent on both error detection and correction, even in the PreHD-B group, our findings are unlikely to be attributable to differences in disease severity or disease stage between patients in the two studies. Given the substantially larger sample of HD expansion-carriers in our study ($n=239$) compared with Lemay et al. ($n=13$), we had greater power to detect any difference in the magnitude of error detection and correction delays relative to healthy controls. The pattern of data was also inconsistent with our predictions of relatively greater delays in error detection in HD. Our hypothesis was based on lines of evidence of striatal involvement in error detection (Falkenstein et al., 2001) and in altering motor actions in response to environmental cues (Marsden & Obeso, 1994), as well as dysmetric overshooting in HD patients (Carella et al., 2003). However, accurate and efficient error correction is also reliant on adjusting motor actions in response to environmental cues and may also be impacted by dysmetric overshooting. Therefore, while different mechanisms underly error detection and error correction, HD-related cognitive and motor deficits appear to contribute to delays in both.

For consistency with the Lemay et al. (2005) study, our study used only the dominant hand. Future studies could investigate whether using the non-dominant hand to examine circle-tracing performance may yield stronger findings, as is suggested by previous findings revealing greater sensitivity of the non-dominant hand to visuomotor integration impairments (Oepen, Mohr, Willmes, & Thoden, 1985).

Our findings demonstrate significant, early deficits in visuomotor integration, which are detectable even in premanifest HD. With replication of these findings, and extension to longitudinal time points, tests of visuomotor integration may become useful as outcome measures in studies of interventions to reduce HD symptoms or modify disease progression. Visuomotor integration and transformation are abilities that warrant further investigation in HD given their functional relevance in daily life.

Acknowledgements

TRACK-HD is supported by the CHDI/High Q Foundation, Inc., a non-for-profit organization dedicated to finding treatments for Huntington's disease. The authors offer their gratitude to the volunteers who participated and to their families and companions who helped to make their participation possible. We also thank Melissa C. Campbell for her excellent editorial assistance on the preparation of this manuscript.

References

Boulet, C., Lemay, M., Bedard, M. A., Chouinard, M. J., Chouinard, S., & Richer, F. (2005). Early Huntington's disease affects movements in transformed sensorimotor mappings. *Brain and Cognition*, *57*(3), 236–243.

- Burton, H., & Sinclair, R. J. (2000). Attending to and remembering tactile stimuli: A review of brain imaging data and single-neuron responses. *Journal of Clinical Neurophysiology*, *17*(6), 575–591.
- Carella, F., Bressanelli, M., Piacentini, S., Soliveri, P., Geminiani, G., Monza, D., et al. (2003). A study of arm movements in Huntington's disease under visually controlled and blindfolded conditions. *Neurological Sciences*, *23*(6), 287–293.
- Falkenstein, M., Hielscher, H., Dziobek, I., Schwarzenau, P., Hoormann, J., Sundermann, B., et al. (2001). Action monitoring, error detection, and the basal ganglia: An ERP study. *Neuroreport*, *12*(1), 157–161.
- Georgiou, N., Bradshaw, J. L., Phillips, J. G., Chiu, E., & Bradshaw, J. A. (1995). Reliance on advance information and movement sequencing in Huntington's disease. *Movement Disorders*, *10*(4), 472–481.
- Hefter, H., Homberg, V., Lange, H. W., & Freund, H. J. (1987). Impairment of rapid movement in Huntington's disease. *Brain*, *110*(3), 585–612.
- Huntington Study Group (1999). Unified Huntington's Disease Rating Scale-99.
- Langbehn, D. R., Brinkman, R. R., Falush, D., Paulsen, J. S., & Hayden, M. R. (2004). A new model for prediction of the age of onset and penetrance for Huntington's disease based on CAG length. *Clinical Genetics*, *65*(4), 267–277.
- Lemay, M., Chouinard, S., Richer, F., & Lesperance, P. (2008). Huntington's disease affects movement termination. *Behavioural Brain Research*, *187*(1), 153–158.
- Lemay, M., Fimbel, E., Beuter, A., Chouinard, S., & Richer, F. (2005). Sensorimotor mapping affects movement correction deficits in early Huntington's disease. *Experimental Brain Research*, *165*(4), 454–460.
- Liang, K. Y., & Zeger, S. L. (1986). Longitudinal data analysis using generalized linear models. *Biometrika*, *73*(1), 13–22.
- Marsden, C. D., & Obeso, J. A. (1994). The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. *Brain*, *117*(4), 877–897.
- Nelson, A. J., Staines, W. R., & McIlroy, W. E. (2004). Tactile stimulus predictability modulates activity in a tactile-motor cortical network. *Experimental Brain Research*, *154*(1), 22–32.
- Oepen, G., Mohr, U., Willmes, K., & Thoden, U. (1985). Huntington's disease: Visuomotor disturbance in patients and offspring. *Journal of Neurology, Neurosurgery and Psychiatry*, *48*(5), 426–433.
- Penney, J. B., Vonsattel, J. P., MacDonald, M. E., Gusella, J. F., & Myers, R. H. (1997). CAG repeat number governs the development rate of pathology in Huntington's disease. *Annals of Neurology*, *41*(5), 689–692.
- Quinn, L., Reilmann, R., Marder, K., & Gordon, A. M. (2001). Altered movement trajectories and force control during object transport in Huntington's disease. *Movement Disorders*, *16*(3), 469–480.
- Rosas, H. D., Hevelone, N. D., Zaleta, A. K., Greve, D. N., Salat, D. H., & Fischl, B. (2005). Regional cortical thinning in preclinical Huntington disease and its relationship to cognition. *Neurology*, *65*(5), 745–747.
- Rosas, H. D., Liu, A. K., Hersch, S., Glessner, M., Ferrante, R. J., Salat, D. H., et al. (2002). Regional and progressive thinning of the cortical ribbon in Huntington's disease. *Neurology*, *58*(5), 695–701.
- Shoulson, I., & Fahn, S. (1979). Huntington disease: Clinical care and evaluation. *Neurology*, *29*(1), 1–3.
- Smith, M. A., Brandt, J., & Shadmehr, R. (2000). Motor disorder in Huntington's disease begins as a dysfunction in error feedback control. *Nature*, *403*(6769), 544–549.
- Tabrizi, S. J., Langbehn, D. R., Leavitt, B. R., Roos, R. A. C., Durr, A., Craufurd, D., et al. (2009). Biological and clinical manifestations of Huntington's disease in the longitudinal TRACK-HD study: Cross-sectional analysis of baseline data. *The Lancet Neurology*, *8*(9), 791–801.
- UNESCO (1997). International Standard Classification of Education from http://www.uis.unesco.org/ev.php?ID=3813_201&ID2=DO_TOPIC.

Glossary

- CAG: cytosine-adenine-guanine
 CI: confidence intervals
 DARTEL: diffeomorphic image registration
 FA: flip angle
 FOV: field of view
 GEE: generalized estimating equations
 HD: Huntington's disease
 ISCED: International Standard Classification of Education
 M: mean
 mm: millimeter
 ms: millisecond
 MRI: magnetic resonance imaging
 SD: standard deviation
 SPM: statistical parametric mapping
 TE: echo time
 TR: repetition time
 UHDRS: Unified Huntington's Disease Rating Scale
 VBM: voxel-based morphometry