

EARLY HUNTINGTON'S DISEASE AFFECTS
MOVEMENTS IN TRANSFORMED SENSORIMOTOR MAPPINGS

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Running head: Sensorimotor transformations in HD

Abstract

This study examined the effect of transformed visual feedback on movement control in Huntington's disease (HD). Patients in the early stages of HD and controls performed aiming movements towards peripheral targets on a digitizing tablet using an indirect visual control of movement through a monitor and emphasizing precision. In a baseline condition, HD patients were slower but showed few precision problems in aiming. When visual feedback was inverted in both vertical and horizontal axes, patients showed problems in initial and terminal phases of movement where feedback is most critical. When visual feedback was inverted along a single axis as in a mirror-inversion, HD patients showed large deviations and over-corrections before adaptation. Adaptation was similar in both groups. These results suggest that HD impairs on-line error correction in novel movements.

Key words: Voluntary movement, planning, sensorimotor adaptation, visuomotor mapping, attention, cognitive control.

In Huntington's disease (HD), neurodegenerative processes centered in the striatum produce significant impairments in cognition, movement, and behavior. Impairments in voluntary movement appear early in HD and are often similar to those seen after damage to premotor or prefrontal cortex. HD patients show problems planning and selecting movements especially when response selection requires attention such as in sequential responses, novel contexts or when interference from competing responses is present (Agostino, Berardelli, Formica, Accornero, & Manfredi, 1992; Bradshaw et al., 1992; Curra et al., 2000; Georgiou, Bradshaw, Phillips, Chiu, & Bradshaw, 1995; Girotti, Marano, Soliveri, Geminiani, & Scigliano, 1988; Gordon, Quinn, Reilmann, & Marder, 2000; Jahanshahi, Brown, & Marsden, 1993; Phillips, Chiu, Bradshaw, & Lansak, 1995; Sprengelmeyer, Lange, & Homberg, 1995; Thompson et al., 1988).

HD patients can also show problems in visually-guided movements. In complex movements, they have problems making transitions between movement segments (Gordon et al., 2000; Quinn, Reilmann, Marder, & Gordon, 2001; Schwarz, Fellows, Schaffrath, & Noth, 2001). In simple visually-guided movements, HD patients show fewer precision problems. However, they are slower than controls, and they show multiple acceleration-deceleration phases to reach a target (Phillips et al., 1996). Movements in HD are also sensitive to concurrent tasks which increase attention demands (Georgiou, Phillips, Bradshaw, Cunnington, & Chiu, 1997). They also show irregularity in the late portion of rapid aiming movements, which suggests on-line error correction problems (Smith, Brandt, & Shadmehr, 2000), but recent evidence suggests that the problem may be specific to larger consciously detected errors (Desmurget et al., 2004).

Simple visually-guided movements are often well-practiced and require little attention except at the beginning and end (Posner & Keele, 1969). Attention-based selection problems in HD could affect movements in novel contexts because of the lack of well-learned

sensorimotor associations to guide movement selection. There are indications that HD patients show problems in novel movements. For example, they cannot maintain normal precision levels in tracking moving targets except at very low speed (Gabrieli, Stebbins, Singh, Willingham, & Goetz, 1997; Heindel, Butters, & Salmon, 1988; Heindel, Salmon, Shults, Walicke, & Butters, 1989; Willingham, Koroshetz, & Peterson, 1996). The goal of the present studies was to test the effects of HD on the control of novel movements in transformed sensorimotor mappings.

Methods

Subjects

Ten patients diagnosed with early-stage Huntington's disease (HD; 1-5 yrs post-diagnosis) were compared to ten controls with no history of cerebral damage matched in age (mean age: 44 years). Table 1 presents clinical data on the HD patients. Motor, cognitive and behavioral symptoms were evaluated by experienced professionals using the Unified Huntington's Disease Rating Scale (Huntington Study Group, 1996). All subjects had normal or corrected-to-normal vision and were right handed. For all subjects, written informed consent to participate in the study was obtained according to the rules of the hospital.

Apparatus and Procedure

Subjects had to move a pen on a digitizing tablet (30 cm X 30 cm) from a central point to a fixed peripheral target using their right hand. The task was controlled by a computer and the position of the pen on the tablet was sampled at a rate of 12 Hz. Subjects controlled their movements through an indirect visual feedback on a monitor placed 1.0 m in front of them and an occluding screen hid the arm from view. The cursor and targets were respectively represented on the monitor by a red spot (1 cm-diameter) and a white circle (2 cm-diameter). All movements began at the centre of the screen and targets appeared in one of four peripheral positions, 40° above or below the horizontal axis on the right or left of midline. These target

positions were chosen because oblique movements are poorly performed before adaptation and require several corrections when feedback is inverted along a single axis (Cunningham, 1989; Petersik & Pantle, 1982).

Subjects were tested in three conditions. In the baseline condition, there was little transformation of visuomotor space except the usual transformation of the horizontal tablet surface to the vertical monitor surface. In this condition, reaching movements are usually executed rapidly and in a straight line. In the full inversion condition, both horizontal and vertical directions of the cursor were inverted in relation to pen movement. To reach the target on the screen, the subject had to move the pen in the opposite direction on the tablet (e.g. lower-left instead of upper-right). This full inversion of movement direction requires only a brief adaptation from natural mapping because it preserves the axis of movement and only changes the polarity of the relationship of visual to proprioceptive signals. In controls, this leads to few small-amplitude trajectory deviations occurring mostly when movement direction must be selected at the beginning of the movement and during terminal adjustments.

In the single-axis inversion condition, the motion of the cursor on the screen was inverted in the vertical axis but not in the horizontal axis. Movements in single-axis inversion produce a significant conflict between visual and proprioceptive feedback. Adaptation to this transformation requires acquisition of a new visuo-motor coordination pattern that is highly distinct from natural movements and significant trajectory deviations are observed during several trials before adaptation takes place (Cunningham, 1989). The peripheral target remained present for the entire duration of the trial: 3.0 s in the baseline condition, 6.0 s in the full inversion condition, and 11.0 s in the single-axis inversion condition.

Subjects were tested in a fixed sequence of conditions: After 8 practice trials, subjects performed 24 trials in the baseline condition, 48 trials in the full inversion condition, 16 more trials in the baseline condition to eliminate the effect of the full inversion, and 64 trials in the single-axis inversion condition. Adjacent conditions were separated by short pauses. Before the

mapping transformations, subjects were told that the task was changed but were not told the specific nature of the change. Instructions emphasized precision over speed. Each target position was presented once in every quadruplet of four consecutive movements in a pseudo-random order. To average out differences between target directions, performance measures (precision and speed) were analyzed using the median of each trial quadruplet. Movement precision was measured by the length of the trajectory of each movement. Movements with short trajectories (<30 cm) which ended at less than 50% of the distance to the target were eliminated (8 trajectories out of 1120 in patients).

Results

Figure 1 shows sample trajectories for the three conditions of the aiming task in controls and in patients. Median trajectory length and average movement speed were computed for each consecutive trial quadruplet in the three conditions. Figure 2 depicts trajectory length and average speed across trials.

- Figs. 1 and 2 here -

In the baseline condition, HD patients showed trajectories that were similar in precision to that of controls ($t(18) = 1.8$, ns). Also, HD patients showed significantly lower average speed than controls ($t(18) = 2.9$, $p < .01$). However, there was no significant difference between the two groups in peak velocity averaged over the baseline trials (Controls: 41.7 ± 18.7 mm/s; HD: 33.6 ± 14.5 mm/s; $t(18) = 1.1$, ns).

In the full inversion condition, patients and controls showed longer trajectories than in the baseline condition in the first adaptation trials. A comparison of trajectory length in the first trial quadruplet of the full inversion condition to the baseline condition showed a significant effect of condition, $F(1,18) = 15.4$, $p = .001$, and group $F(1,18) = 4.17$, $p = .05$, as well as a non

significant trend for the group X condition interaction, $F(1,18) = 3.2$, $p = .09$. The practice effect was examined through the difference between the first and last trial quadruplets. This analysis revealed a significant effect of group, $F(1,18) = 4.4$, $p = .05$, a significant effect of practice, $F(1,18) = 8.9$, $p < .01$, but no significant interaction, $F(1,18) = 0.7$, ns.

Errors in the initial selection of movement direction were determined for the last 16 trials of the full inversion condition. These errors were defined as movement initiated in the direction opposite to the movement's main axis. Errors in the initial selection of movement direction occurred more often in patients than controls (28.8% and 7.5% of the total number of trials in patients and in controls respectively), $F(1, 18) = 6.9$, $p = .02$.

Also, the trajectory was segmented in five parts in order to determine whether the longer trajectory observed in HD patients was uniformly distributed along the movement. This segmentation was done for the last 16 trials of the full inversion condition. Each segment corresponds to 20% of the vectorial distance between the starting base and the target. The results clearly showed that the first and last segments were longer in HD patients (6.2 mm and 7.8 mm for the first and the last segments respectively) than in controls (4.4 mm and 3.4 mm for the first and the last segments respectively) whereas the second, third and fourth segments were similar between groups (Controls: 3.2, 2.8, 2.5 mm; Patients: 3.4, 3.1, 3.2 mm for the second, third and fourth segments respectively), $F(4,72) = 7.31$; $p < .0001$.

Average speed was highly variable. Patients were often slower than controls, except in the first trials of each transformation. An ANOVA on average speed in the first and last trial quadruplets revealed a significant effect of practice, $F(1,18) = 23.5$, $p < .01$, but no significant effect of group, $F(1,18) = 2.3$, ns, and the interaction showed only a trend, $F(1,18) = 4.0$, $p = .06$. A comparison of average speed in the first trial quadruplet to that in the baseline condition showed a significant effect of condition, $F(1,18) = 43.5$, $p < .001$, a significant effect of group, $F(1,18) = 6.05$, $p = .02$, and a significant interaction, $F(1,18) = 7.8$, $p = .01$. Simple effects

showed that groups did not significantly differ in average speed in the first trials of the full inversion condition, $t(18) = -0.4$, ns, but did differ in the baseline condition $t(18) = -2.9$, $p = .01$.

The after-effect of the full inversion condition was examined using the first quadruplet of the baseline condition which followed the full inversion condition. In that condition, patients showed significantly longer trajectories than controls, $F(1,18) = 4.7$, $p = .04$ and were significantly slower than controls, $F(1,18) = 4.6$, $p = .05$.

When the visuomotor mapping was inverted along a single axis, HD patients showed very long movement trajectories on the first trials. The trajectories of HD patients contained larger and more frequent deviations than that of controls. Some movement segments were roughly in the axis of the visually perceived target (the natural visuomotor mapping), but other segments showed a great variety of directions and trajectories. The comparison of the first trial quadruplet to baseline aiming showed a significant effect of group, $F(1,18) = 36.2$, $p < .001$, a significant effect of condition, $F(1,18) = 104.9$, $p < .001$, and a significant interaction, $F(1,18) = 32.5$, $p < .001$. Simple effects showed that groups differed markedly in the first trials of the single-axis inversion condition, $t(18) = 5.9$, $p < .001$, in contrast to the baseline condition, $t(18) = 1.8$, $p = .09$. An analysis of the effect of practice on trajectory length in the first and last trial quadruplets revealed a significant effect of group, $F(1,18) = 32.1$, $p < .01$, a significant effect of practice, $F(1,18) = 78.2$, $p < .01$, and a significant group-by-trial interaction, $F(1,18) = 17.6$, $p < .01$ (which may be due to a floor effect in controls). Simple effects showed that both groups improved their performance with practice (Controls: $t(9) = 4.5$, $p = .001$; patients: $t(9) = 9.2$, $p < .001$). A separate analysis examined whether practice reduced trajectory length to the level of baseline performance by comparing average trajectory length in the last trial quadruplet of the single-axis inversion condition to that of the baseline condition. This analysis showed a significant effect of group, $F(1,18) = 13.0$, $p < .01$, a significant effect of condition, $F(1,18) = 16.4$, $p < .01$, and a significant interaction, $F(1,18) = 10.8$, $p < .01$. Simple effects showed that while controls reduced their trajectory lengths to near baseline levels, patients still performed

worse than in the baseline condition after 64 practice trials (Controls: $Z = 1.0$, $p = .31$; HD: $Z = 2.8$, $p < .01$).

In the single-axis inversion condition, HD patients appeared to move faster than controls at first. We compared average speed in the first trial quadruplet to that in the baseline condition (mean value). This analysis showed no significant effect of group, $F(1,18) = 1.7$, ns, but a significant effect of condition, $F(1,18) = 62.0$, $p < .001$, and a significant interaction $F(1,18) = 16.9$, $p = .001$. Simple effects showed that patients reduced their speed less than controls (patients $t(9) = 2.9$, $p = .02$; controls $t(9) = 7.9$, $p < .001$). An ANOVA on average speed revealed no significant effect of group, $F(1,18) = 0.44$, $p = .52$, but a significant effect of practice, $F(1,18) = 6.4$, $p = .02$, and a significant group-by-trial interaction, $F(1,18) = 15.1$, $p < .01$. Simple effects showed that while controls increased their average speed with practice, HD patients showed little increase in speed (Controls: $Z = 2.7$, $p < .01$; HD: $Z = 1.3$, $p = .20$). We also computed the peak velocity in the first eight trials of the single-axis inversion condition. Controls showed a significantly lower peak velocity than HD patients (Controls: 18.9 ± 4.2 cm/s; HD: 35.9 ± 10.1 cm/s; $t(18) = 4.9$, $p < .01$). There were no significant differences between medicated and unmedicated patients on any of the measures examined.

Discussion

In the baseline condition, HD patients and controls showed movement trajectories that were almost as precise. This confirms previous observations on aiming movements in HD (Georgiou et al., 1997; Phillips et al., 1996) and indicates that the basic task of reaching a relatively large target on a screen with a horizontal arm movement is performed with adequate precision by HD patients when precision was emphasized. As expected, patients were slower than controls.

When visual feedback of movement was inverted in both horizontal and vertical axes, subjects had to learn to reverse the direction of movement. These movements required only a

brief adaptation because they preserve the axis of the standard visuomotor coordination. In this condition, HD patients showed less precision than controls and most of the precision deficit was linked to the initial selection of the reversed direction and at the terminal phase when error final directional adjustments based on error feedback are necessary. This indicates that patients show movement selection errors, which are in line with errors observed in choice responses when competing responses are present. Many deviations also occurred in the last portion of the trajectory, which is consistent with an error correction problem in HD (Smith et al., 2000). These results indicate that difficulties occur in patients mainly during the attention demanding portions of the movement.

In the single-axis inversion, the standard coordination pattern between visual, proprioceptive and motor signals had to be inhibited and replaced with voluntary corrections based on error feedback. In this condition, HD patients showed significant precision problems. This problem cannot be attributed to basic sensory or motor execution difficulties or to spatial orientation problems since patients were as accurate as controls in the baseline condition with targets of identical size and distance. Also, this performance is not due to an inability to initiate and execute movement segments to obtain feedback since patients generally executed large and frequent movement segments. Moreover, the problem cannot solely be explained by perseverative tendencies because corrections were made in multiple directions.

One may suggest that the results could be due to an impaired access to proprioceptive information in HD. HD patients can show abnormal somatosensory processing (Abbruzzese, Dall'Agata, Morena, Reni, & Favale, 1990; Boecker et al., 1999; Kuwert et al., 1993; Topper, Schwarz, Podoll, Domges, & Noth, 1993). However, in patients with somatosensory deafferentation, impaired proprioception can actually facilitate mirror-inverted movements (Lajoie et al., 1992). In situations involving a visuo-proprioceptive conflict, a proprioceptive impairment attenuates the sensory conflict, helping the subject rely only on visual error signals. Also, the large effect of practice in mirror-inverted aiming suggests that HD patients have

access to proprioceptive information. Thus, a proprioceptive impairment does not appear to be critical in producing the impairment observed here.

The data indicate that HD affects movements in transformed visuomotor mappings. These results are similar to what was observed in patients with frontal cortex lesions (Richer et al., 1999). The problem is more pronounced when error feedback is more essential and it is reduced with practice. These observations suggest that the problem lies in the control of movement with high attention demands. In this task, attention may be used to inhibit the standard mapping as well as to facilitate movement selection based on error feedback. More work will of course be needed to disentangle these contributions if possible. This hypothesis is compatible with impairments in attention and choice responses in these patients (Bradshaw et al., 1992; Hefter, Homberg, Lange, & Freund, 1987; Jahanshahi et al., 1993; Lawrence et al., 1996). The results are similar to the problems shown by HD patients in the Stroop task, in which an overlearned skill (word reading) interferes with an attention-demanding voluntary response (rapid color naming) (ex: Snowden et al., 2001). The results are also compatible with previous data showing deleterious effects of a concurrent task on movements in HD, since concurrent tasks like novel contexts increase attention demands (Georgious et al., 1997). Variables such as novelty, interference, and other task demands may recruit processes which help select the appropriate movement on the basis of error feedback when predictive control processes based on acquired skills are insufficient to perform the task adequately (Fuster, 1997; Miller & Cohen, 2001).

Smith et al. (2000) described a deficit in on-line error correction in HD in rapid aiming movements. In Parkinson's disease patients, Desmurget et al. (2004) showed that the problem may be specific to larger consciously detected errors. Our results support the proposition of Smith et al. (2000) and further it by showing a similar deficit for attention demanding movement performed more slowly. The present data suggest that the deficit in on-line control may be

linked to the attention demands of the movement. In this sense, this problem could be linked to the general impairments in attention and decisional (executive) control in frontostriatal disorders.

In novel tasks, reducing speed can help accuracy by reducing the amplitude of deviations as well as improving the control of corrections. HD patients did not slow down as much as controls in single-axis inversion. However, HD patients can reduce the speed of their movements to improve precision in other movement tasks (Boulet, Lafrance, Chouinard, Lesperance, & Richer, 2001). Thus, their higher speed in novel movements may be a consequence of their attention problems, as problems in noticing deviations or selecting efficient corrections may lead to higher average speed.

HD patients showed an improved precision with practice which is consistent with previous reports of relatively good acquisition of mirror drawing movements in these patients (Gabrieli et al., 1997). This improvement with practice contrasts with the poor initial performance of patients. The improved precision suggests that some portions of movement control were taken over by the newly acquired mapping. However, patients still showed some precision problems in single-axis inversion after 64 trials of practice and they did not improve their speed with practice as much as controls. This may indicate that patients still used some degree of attention-based selection to control these movements even after practice. HD patients can show acquisition problems in some tasks such as predictable visuomotor tracking (Gabrieli et al., 1997; Willingham & Koroshetz, 1993; Willingham et al., 1996), but the cause of task differences in acquisition impairments is still unclear.

The present results indicate that HD affects movements mostly early in practice and when attention to error feedback is more essential. These observations suggest that attention or voluntary control difficulties may contribute to the performance of HD patients in skill learning tasks. HD patients may show more acquisition problems in tasks in which attention-based control is critical for many trials before new skills are developed. This will have to be tested directly. Overall, the present data suggest that HD affects error correction in novel movements.

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Table 1. Clinical and demographic data for HD patients.

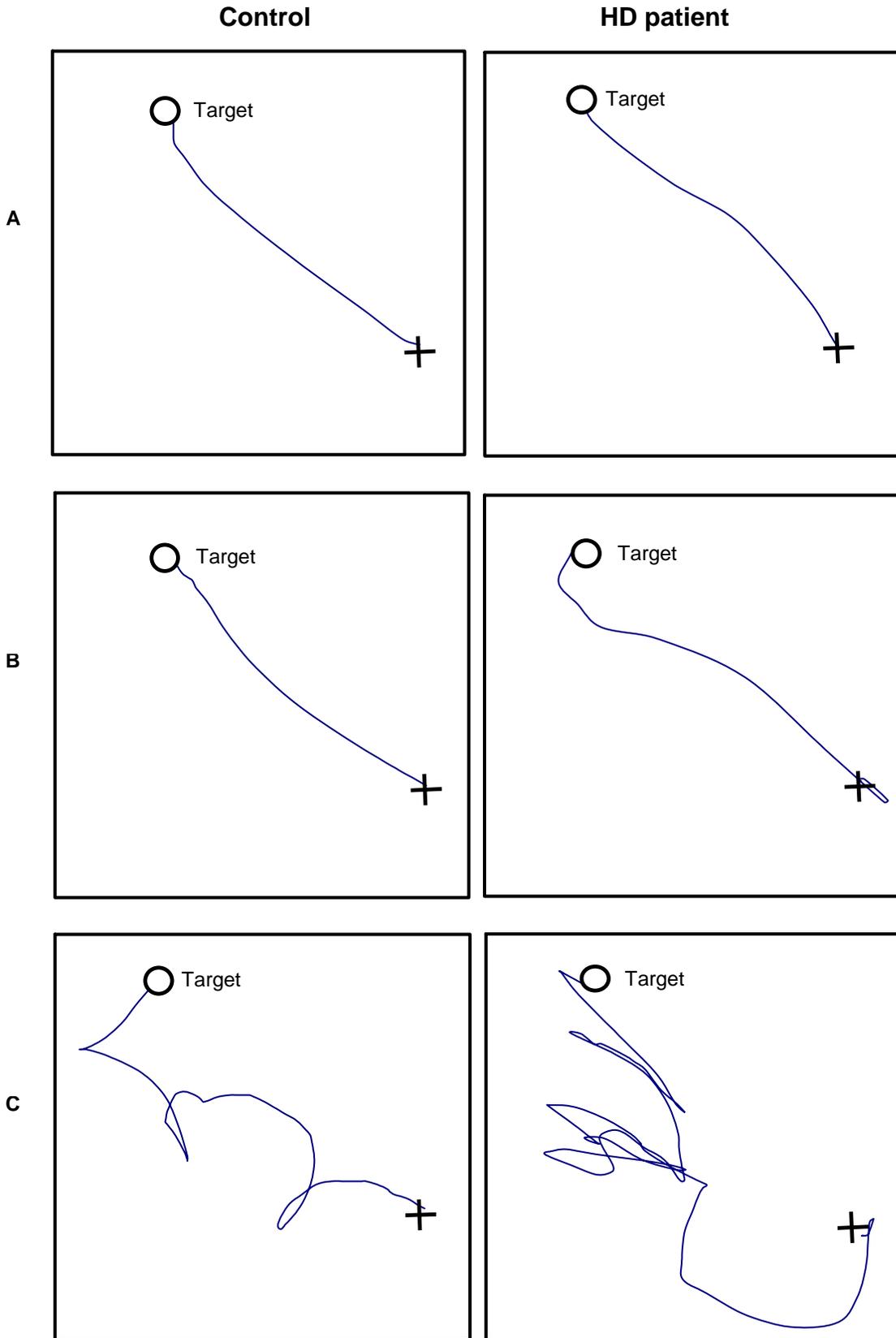
No.	Age (years)	Sex	Duration of symptoms (years)	UHDRS Motor score	UHDRS Cognitive score	Medication
1	41	F	3	20	284	Nil
2	41	M	4	26	192	Nil
3	33	M	2	36	194	Nil
4	50	M	2	35	200	Nefazodone
5	50	M	4	9	198	Serzone
6	53	M	5	54	---	Nil
7	41	M	3	55	180	Nil
8	47	M	2	16	225	Nil
9	58	M	5	26	158	Tetrabenazine, Lorazepam, Paroxetine
10	37	M	3	55	128	Lorazepam, Olanzapine

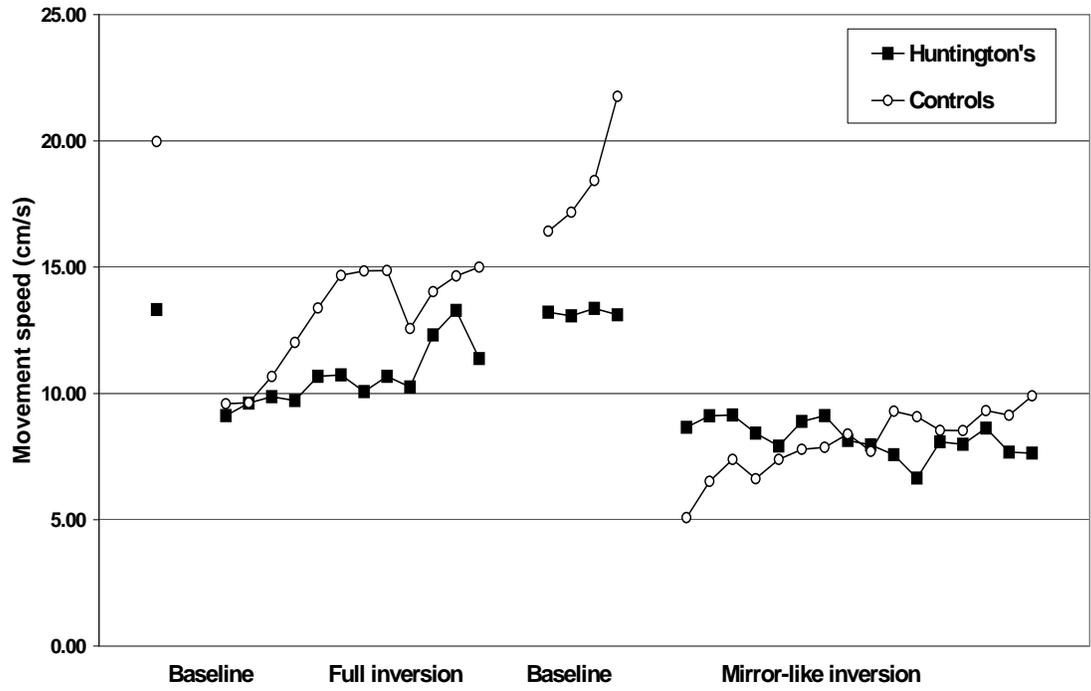
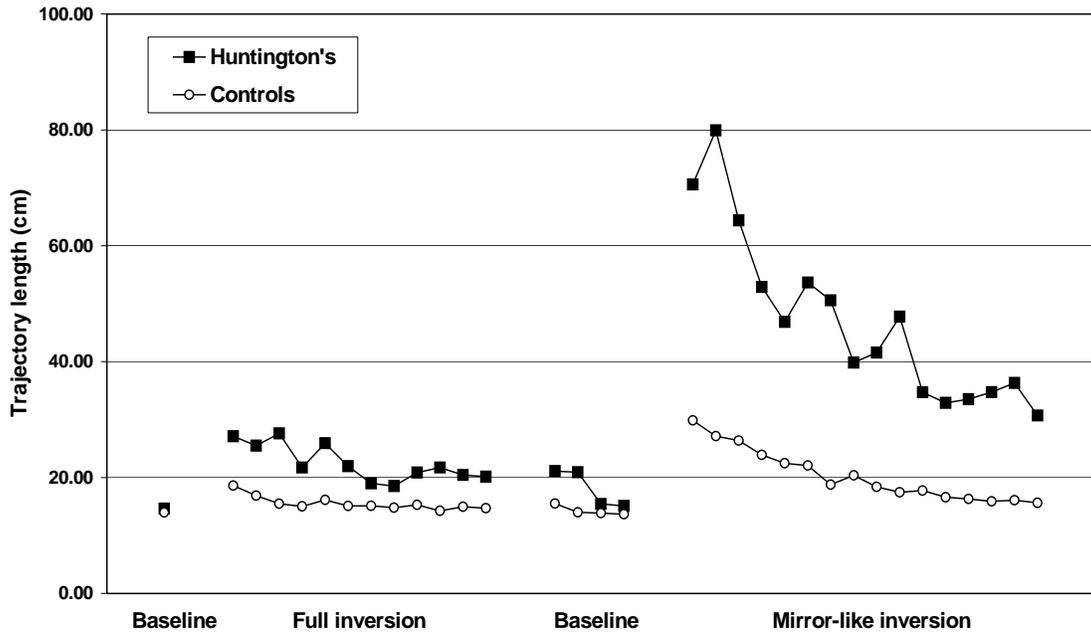
Note: The UHDRS motor score ranges from 0 to 120 where 0 is normal. In the cognitive score, higher values indicate better performance.

Figure Captions

Figure 1. Sample trajectories in the three conditions of the 2-D aiming task in HD patients and controls (A) Baseline aiming, B) Full inversion, C) Single-axis inversion. The trajectories for conditions involving transformed mappings illustrate performance early during adaptation.

Figure 2. Average length (A) and average speed (B) of movement trajectories in the three conditions of the 2-D aiming task. Each point represents a median of four consecutive trials (one trial per target).





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