

ORIGINAL

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A study of arm movements in Huntington's disease under visually controlled and blindfolded conditions

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Abstract The so-called bradykinesia of Huntington's disease (HD) seems not due to reduced movement speed alone but may also be task-dependent. We therefore investigated the influence of visual control on the ability of HD patients to perform a motor task. Ten HD patients, never treated with neuroleptic drugs and with mild functional impairment in activities of daily living, performed the task blindfolded and not blindfolded, as did 10 age- and education-matched healthy controls. The task was to use the dominant hand to trace out the contours of a 20x20 cm square in a clockwise direction, pausing at each corner. The square was marked on the table at which the subject sat. Accuracy was stressed rather than speed. A videocamera-based system recorded movement trajectories, from which kinematic and error parameters were derived. Patients and controls moved at comparable speeds but patients took longer to complete the task due to more curvilinear and hence longer trajectories. Patients spent more time in the deceleration phase of the movement, and in the blindfold condition had more variable movements as indicated by greater error variability scores. Correlation analysis showed that kinematic parameters in patients did not correlate with involuntary movement scores. These findings indicate that abnormalities of motor control are present in HD when movement accuracy (and not velocity) is required. HD patients are more dependent on visual control than normal subjects.

Key words Huntington's disease • Kinematics • Visual control

Introduction

Recent work on voluntary movements performed by patients with Huntington's disease (HD) has suggested that motor impairment in that condition is not restricted to slowing of fast [1, 2] and sequential movements [3, 4] – sometimes referred to as HD bradykinesia [5]. Smith et al. [6] in fact pointed out that HD patients display aberrant responses to both internal and self-generated errors and that their movements are more sensitive to external perturbations than those of controls. Quinn et al. [7] have revealed that slowness of movement in HD is not consistently observed during transport of an object, so that the various phases of movement are affected differently [7]. Therefore, we thought it of interest to investigate the influence of visual control on reaching movements of HD patients by means of a motor task that required accuracy rather than speed.

Subjects and methods

Ten genetically confirmed HD patients (4 men, Table 1) and 10 age-matched controls (4 men) were enrolled in the study. Mean age of controls was 52.8 years (range, 41–68) and mean education was 11.9 years (range, 5–18).

The patients were assessed with the Unified Huntington's disease rating scale (UHDRS) [8] and the mini-mental state examination (MMSE) [9]. All had a UHDRS functional score above 9, none had significant psychiatric disorders, and none had been treated with neuroleptics. The UHDRS and MMSE were administered to patients not more than one week before the kinematic assessment. The UHDRS global motor score and the chorea subscore were calculated. Informed consent to take part in the study was obtained from all subjects.

Motor task

Subjects performed the motor task twice, once under visual control and once blindfolded. The order of performance (visual vs. blind-

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Table 1 Clinical characteristics of 10 patients with Huntington's disease

Patient	Sex	Age, years	Education, years	MMSE score	Disease duration, years	UHDRS scores		
						Functional capacity	Global motor	Chorea
1	F	62	8	26	4	9	44	11
2	F	58	13	25	8	12	22	7
3	M	54	13	28	4	11	23	7
4	F	54	13	27	5	11	19	4
5	M	43	13	27	4	13	13	8
6	F	47	8	25	2	12	19	3
7	M	57	13	29	3	12	23	7
8	F	42	13	22	6	11	40	12
9	F	61	5	22	5	11	33	5
10	M	46	18	28	2	12	19	9

MMSE, mini-mental state examination; *UHDRS*, unified Huntington's disease rating scale

folded) was random in each group. To perform the task, the subject sat at a table on which four spots 3 cm in diameter had been marked, defining the corners of a 20-cm square. A plastic rod, on which a reflector 3 cm in diameter had been mounted at the tip, was held in the dominant hand and the subject was instructed to trace out, using the rod, the four corners of the square in a clockwise direction, starting from the bottom right corner. Subjects were instructed to perform the task as precisely as possible (rather than as quickly as possible), pausing momentarily at each corner so that the task consisted of four distinct movements. The corner spots marked where the direction of movement had to change. Subjects were further instructed to begin at will after a tone that followed, by 2–5 seconds, a warning given by the examiner to be ready. There were 20 repetitions in each condition and the performance of these was separated by a pause of about two minutes. In both conditions subjects were allowed as many practice trials as they wanted or needed in the examiner's opinion before starting the experimental session. Since the task was simple, not more than 15 minutes were usually required before the subject and examiner felt the task could begin. The procedure was approved by the ethics committee.

Apparatus and data acquisition

The positions of the corners of the square on the table and the trajectories of the rod (and hence arm movements) were recorded using a high-definition system employing two videocameras with a sampling frequency of 50 Hz (McReflex, Qualisys, Partille, Sweden). Before starting each test, four reflective markers were placed on the corners of the square and their spatial coordinates were recorded in relation to the McReflex reference system established by a prior calibration procedure. The markers were then removed and the tracing task began. The movements of the reflector mounted on the rod were recorded as a sequence of spatial co-ordinates in relation to the reference system. Tangential velocities were then calculated as the derivative of movement with respect to time. To reduce noise, a mobile averaging method on three frames was applied to the velocity at each measurement time.

Experimental measures

Two kinds of measures of motor task performance were obtained: kinematic parameters and target errors.

Kinematic parameters were calculated from the velocity profile

for each of the four sub-movements (from one corner of the square to the next). The beginning of a sub-movement was recognized when the velocity first reached 50 mm/s; its end was recognized when the velocity fell below this value and remained below it for at least 150 ms. These characteristics were recognized by an algorithm, however the visual traces of the velocity curves were always inspected by the examiner and the duration of each sub-movement decided from the trace, sometimes resulting in recalculation of the kinematic parameters, particularly for the patients.

The kinematic parameters determined were movement time (MT), peak velocity (PV), mean velocity (MV), percentage of time in acceleration phase (PAT), linearity ratio (LR) and distance traveled (DT). MT was defined as the time from the beginning to the end of each sub-movement. PV was defined as the highest instantaneous velocity during each sub-movement. MV was the average of the velocities in each sub-movement. PAT was determined by dividing the time from the start of movement to the time of peak velocity by MT and multiplying by 100. LR was calculated for each sub-movement as the ratio of the actual distance traveled to the shortest distance between the start and end times of each sub-movement. A value of 1 indicates a perfectly linear path and a ratio greater than 1 a curved path. DT refers to the distance traveled by the tip of the rod during each sub-movement. These parameters were calculated for each of the four sub-movements and averaged for each movement. The first ten consecutive valid movements performed in each condition were used for the statistical analysis. A trial was judged invalid if a subject anticipated the go signal or failed to stop for at least 150 ms at each corner.

We calculated tangential error (TE) and lateral error (LE) for each sub-movement. The tangential error was measured relative to the target corner of the square and was considered positive when the rod was moved past the corner (overshoot) and negative when the rod did not reach the corner (undershoot). The lateral error was measured relative to the line joining the departure corner to the target corner, and was positive for outward displacement, and negative for inward displacement. Two estimates of target error were obtained for TE and LE in each subject. One was error bias, calculated as the average TE (TEB) and LE (LEB) for the ten valid movements for each condition; the second was error variability, calculated as the mean standard deviation of TE (TEV) and LE (LEV) for the ten valid movements.

Statistical analysis

The experimental variables were analyzed using non-parametric statistics due to non-normal distribution of the data. Descriptive sta-

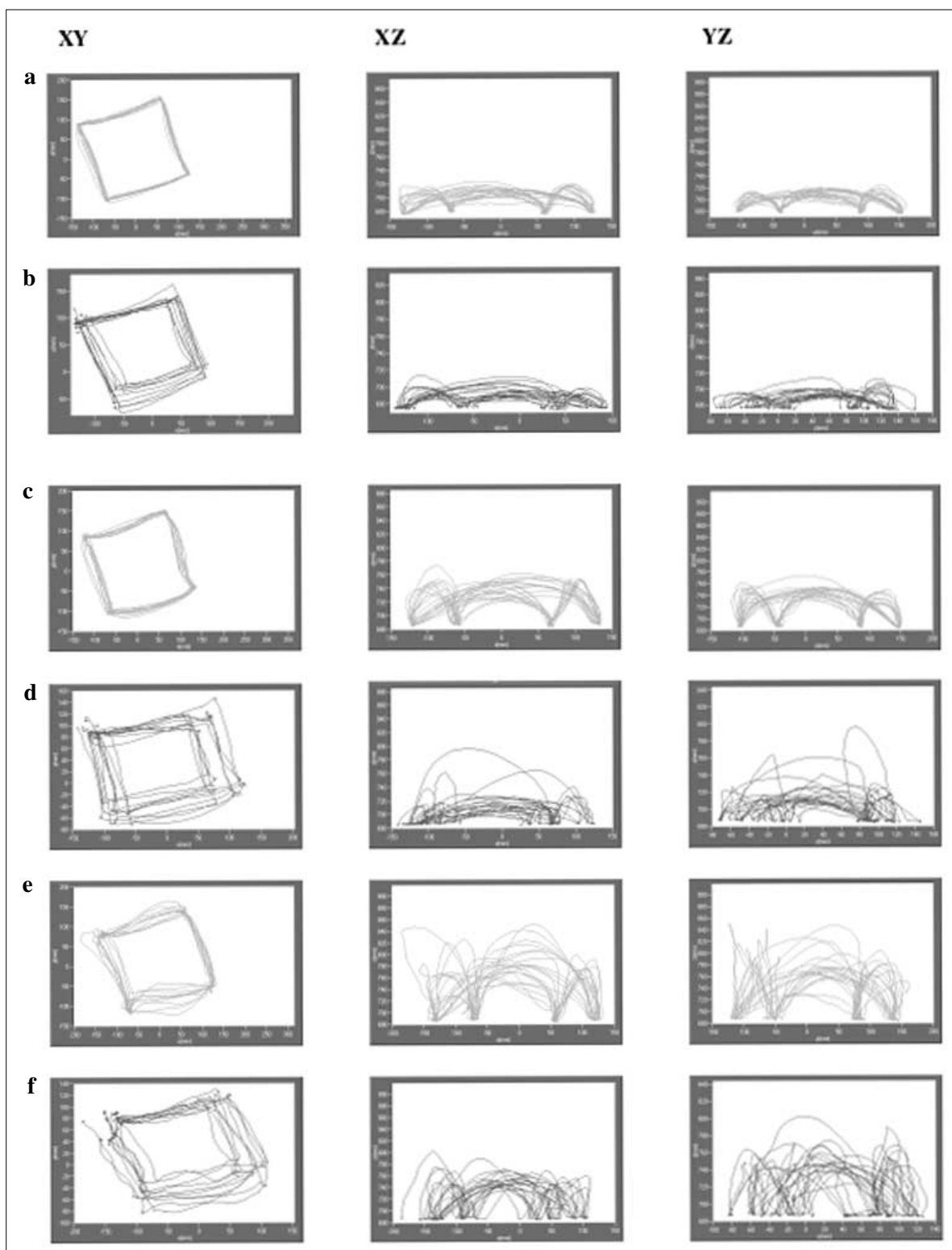


Fig 1a-f Trajectory outlines in controls and patients with Huntington's disease. The graphs show movements in XY (left panels), XZ (center panels) and YZ (right panels) planes of the McReflex system of reference. The XY plane is horizontal. **a, b** Control subject. Note the regularity of movement under visual control (a) while in the blindfolded condition (b) the variation in trajectories increases as do the errors in reaching the corners (mainly undershooting); nevertheless the overall regularity of the movements is preserved. **c, d** Performance of a particularly mildly affected patient (UHDRS global motor score, 19). Under visual control (c), her movement trajectories are more curved and more variable than those of the control (a); when blindfolded (d) trajectory variability becomes more marked and includes some very highly curved movements. There is also greater variation of errors. **e, f** Trajectories produced by a more severely impaired patient (UHDRS global motor score, 40). Increased irregularity of movement compared to the mildly affected patient is already evident under visual control (e). **f** Blindfolded condition

tistics are reported as medians and interquartile ranges. The Mann-Whitney U test was used to compare patient and control data. Wilcoxon's signed-rank test was used to compare subject data in visual control and blindfold conditions. Correlations were tested using Spearman's rho. A $p < 0.05$ was considered statistically significant; values of $p < 0.01$ are noted.

Results

Movement trajectories produced by control subjects with visual control were generally uniform, with restricted intra-subject variability. Intersubject variability, possibly reflecting adoption of different movement strategies by different subjects, was contained. The trajectories generated by blindfolded controls were, as expected, more varied than those produced under visual control. Trajectories produced by the HD patients using visual control were characterized by conspicuous inter- and intrasubject variability (Fig. 1). Intersubject variability increased with disease severity, as assessed by UHDRS global motor score. The trajectories produced by blindfolded patients were conspicuously more irregular than those of any blindfolded control (Fig. 1).

The results of kinematic and error scores are summarized in Table 2. Mean velocity did not differ between controls and patients in either condition, in keeping with the instructions received on task accuracy. As expected, mean velocity was higher under visual control than blindfolded in both groups ($p < 0.01$). Similarly, peak velocity was higher in each group under visual control than blindfolded ($p < 0.01$). Peak velocity

was higher in patients than controls under visual control ($p < 0.05$), but not when blindfolded. Notwithstanding comparable speeds, movement times were longer in patients than in controls in both the visual and blindfolded conditions ($p < 0.05$). For each group, movement times under visual control did not differ from blindfolded movement times.

Movements were less linear (LR greater) in patients than controls under both conditions ($p < 0.01$), but within group (not blindfolded vs. blindfolded) differences were not significant. Distance traveled was greater in patients than controls under visual control ($p < 0.01$) and tended to be greater in patients in the blindfolded condition ($p = 0.07$). For each group (controls, $p < 0.01$; patients, $p < 0.05$) distance traveled was greater under visual control than when blindfolded. Finally, the percentage time in the acceleration phase was greater in controls than patients, in both visual and blindfolded conditions ($p < 0.05$), but within group (not blindfolded vs. blindfolded) differences were not significant.

As regards error scores, tangential error bias did not differ between controls and patients in either condition, but was significantly greater in the blindfolded than not blindfolded condition for both controls ($p < 0.01$) and patients ($p < 0.05$). Similarly, the lateral error bias did not differ between controls and patients in either condition, but it was greater when controls ($p < 0.01$) or patients ($p < 0.05$) were blindfolded. Tangential and lateral error variabilities did not differ between groups under visual control but both were significantly greater ($p < 0.05$ and $p < 0.01$, respectively) in patients than controls under blindfolded conditions. In each group TEV and LEV were greater in blindfolded than not blindfolded conditions ($p < 0.01$).

When we analyzed for correlations in kinematic scores

Table 2 Kinematic results in HD patients and controls

	Controls		Patients	
	Not blindfolded	Blindfolded	Not blindfolded	Blindfolded
Movement time, s	0.79 (0.15)	0.80 (0.19)	0.84 (0.24)*	0.92 (0.19)*
Peak velocity, mm/s	592 (145)	425 (102) ^{°°}	680 (145)*	493 (146) ^{°°}
Mean velocity, mm/s	311 (59)	247 (65) ^{°°}	330 (39)	239 (62) ^{°°}
Percentage time in acceleration phase	32.5 (6.5)	36.4 (9.1)	25.5 (7.9)*	26.5 (6.7)*
Linearity ratio	1.14 (0.09)	1.17 (0.14)	1.38 (0.26)**	1.41 (0.33)**
Distance travelled, mm	227 (12)	188 (40) ^{°°}	278 (56)**	216 (42)§°
Tangential error bias, mm	-0.4 (4.0)	-20.1 (14.8) ^{°°}	-1.6 (3.9)	-26.1 (27.5)°
Lateral error bias, mm	0.1 (0.8)	-20.8 (11.2) ^{°°}	-0.2 (0.8)	19.1 (27.2)°
Tangential error variability, mm	6.5 (1.7)	11.4 (3.6) ^{°°}	6.8 (3.0)	15.0 (11.1)* ^{°°}
Lateral error variability, mm	1.7 (0.5)	10.5 (2.6) ^{°°}	1.9 (0.4)	14.6 (5.4)* ^{°°°}

* $p < 0.05$; ** $p < 0.01$; § $p = 0.07$ vs. controls

° $p < 0.05$; °° $p < 0.01$ vs. not blindfolded condition for the same group

under visual control and blindfolded conditions, clear-cut differences were observed between patients and controls. In controls, movement time ($\rho = 0.84$; $p < 0.01$), peak velocity ($\rho = 0.79$; $p < 0.01$), mean velocity ($\rho = 0.64$; $p < 0.05$), percentage of time in the acceleration phase ($\rho = 0.67$; $p < 0.05$) and linearity of movement ($\rho = 0.81$; $p < 0.01$) were all correlated in the visual and blindfold conditions; a borderline significance was found for the distance traveled ($\rho = 0.62$; $p = 0.054$). In patients, only percentage time in the acceleration phase ($\rho = 0.68$; $p < 0.05$) and the linearity of movement ($\rho = 0.66$; $p < 0.05$) were correlated in the visual and blindfold conditions. Error scores under visual control and kinematic scores blindfolded did not correlate between the two conditions in either group. Finally, no correlation existed between the UHDRS chorea subscore and kinematic or error scores.

Discussion

Voluntary movements are altered in HD patients even when speed is not required. This was demonstrated by the longer movement times, more curvilinear trajectories (greater LR) and greater distances traveled compared to controls, although mean and peak velocities were not reduced in patients. We also found that patients spent more time than controls in the deceleration phase of the movement, possibly to compensate for their irregular movements; in fact under visual control patients' error scores were not different from those of controls. However patients' movements worsened markedly in the absence of visual feedback, being characterized by significantly higher scores for tangential and lateral error variability than controls.

Other studies have already documented that HD patients have increased variability of movement duration [10] and more curvilinear trajectories [11] during reaching move-

ments and the question arises of what brings about this irregularity of movement. It is unlikely that chorea significantly contributes to the irregularity of movements in this respect. Phillips et al. [10], for instance, excluded trials containing choreiform movements. In the present study, the lack of correlation between chorea scores and kinematic variables, and also clinical observation of patients during the procedure, made this possibility unlikely. It is noteworthy in this context that other physiological parameters, for example cortical excitability [12, 13], are questionably related to chorea in HD. Interestingly, Smith et al. [6] recently characterized movements in HD patients as subject to abrupt changes in acceleration and hence more jerky than in controls. This jerkiness appears to be a basic motor abnormality in HD as it is present even in asymptomatic carriers, yet correlates with disease severity. They also noted that movement termination was disturbed much more than initiation and that the sensitivity of end-movement jerk to self-generated early errors was greater in HD patients. Also, HD patients were especially sensitive to externally imposed perturbations. We therefore propose that this jerkiness of movement (Fig. 2) is responsible for the conspicuous movement irregularities and hence longer trajectories of reaching moments in HD, possibly due to a dysfunction of the error feedback control system in these patients. Because of these longer trajectories, HD patients take longer to go through equal distances than controls. By definition, bradykinesia refers to slowness of movements of similar amplitude. It appears that the motor abnormality in HD is not only limited to bradykinesia, but it is also present when the movements are performed at a speed similar as in normal subjects.

A second issue concerns the significance of increased visual dependency in HD as we indeed observed that movement accuracy and smoothness markedly deteriorated in blindfolded patients. This deterioration, quantified as significantly greater tangential and lateral error variability, suggests that patients were unable to compensate for their basic

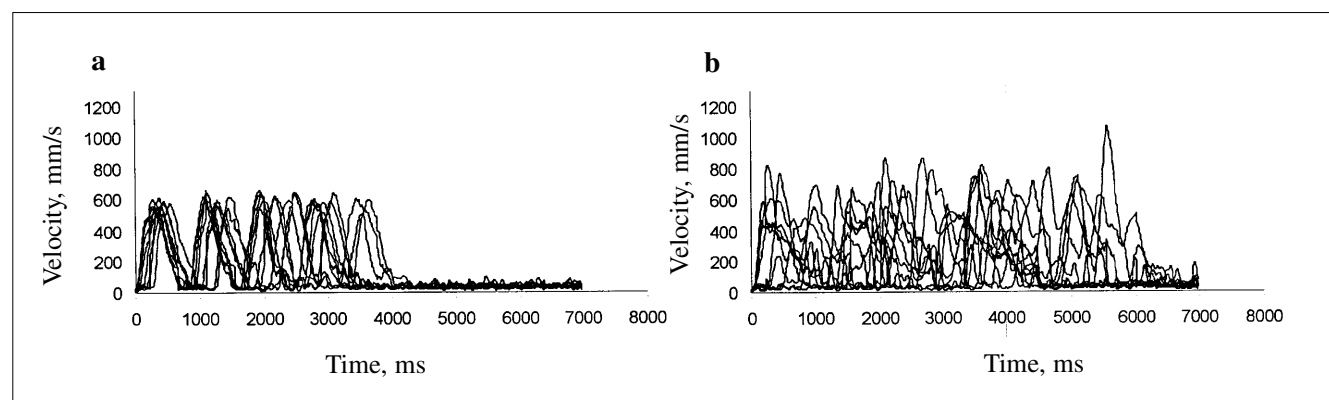


Fig. 2a, b Velocity outlines for each of the four sub-movements under visual control. **a** Healthy control subject. **b** HD patient # 8. Velocity outlines of the patient are manifestly more irregular and variable

movement jerkiness without visual control. It is unlikely that greater error variability was simply due to higher peak velocity in blindfolded conditions since peak velocity was not significantly increased in blindfolded conditions. In contrast, feedback movement control may be defective in HD possibly due to deficits in the afferent signals important for error control. It is known that HD patients have abnormal somatosensory evoked potentials and long-loop transcortical reflexes; therefore signals necessary to correct movements without visual control may be corrupted [14–17].

Finally, it is not known to what extent the present findings are specific for HD. Patients with cerebellar ataxia also performed movements that were more circuitous and of greater length than normal, under visual control [18]. Data from normal subjects suggest that the neocerebellum is involved in monitoring and optimizing movements, making use of sensory feedback, while the basal ganglia are probably concerned with selecting movements or appropriate muscles [19]. However, in HD, sensory input to the cortex is altered, while striatal output to the thalamus (which relays sensory information to the cortex) is also altered. The net effect may be defective proprioceptive feedback control of movements in these patients. To address this issue, further studies are required comparing patients with different clinical conditions.

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Sommario In questo lavoro è stato studiato l'effetto del controllo visivo sulla capacità di pazienti con malattia di Huntington di effettuare un compito motorio. Sono stati studiati dieci pazienti mai trattati con neurolettici e con modesto deficit funzionale e confrontati con altrettanti controlli normali di simile età e scolarità. Tutti i soggetti hanno usato la mano dominante per tracciare i contorni di un quadrato di 20 cm di lato disegnato su di un tavolo di fronte al quale erano seduti. Ai soggetti era richiesto di essere accurati nel movimento piuttosto che massimalmente veloci e di effettuare una breve pausa ad ogni angolo. Questo compito era eseguito mentre i pazienti potevano osservare il quadrato e la propria mano e mentre erano bendati. Un sistema di video camere registrava le traiettorie e permetteva di ottenere parametri cinematici e di errore. L'analisi dei dati dimostrava che i pazienti ed i controlli si muovevano a velocità simili ma i pazienti impiegavano più tempo a completare il percorso a causa di traiettorie più curvilinee e quindi più lunghe. La fase di decelerazione era più prolungata nei pazienti e nella condizione di cecità le loro traiettorie erano significativamente più variabili. I parametri cinematici infine non correlavano con i punteggi dei movimenti involontari. Questo studio dimostra che i pazienti con malattia di Huntington presentano un controllo motorio anomalo non

solo quando si richieda massima velocità ma anche quando è richiesto di compiere un movimento accurato. I pazienti con malattia di Huntington infine sono maggiormente dipendenti dal controllo visivo.

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