Huntington's disease: visuomotor disturbance in patients and offspring

G OEPEL,* U MOHR,† K WILLMES,‡ U THODENT†

From Abteilung Allgemeine Psychiatrie* and Abteilung Klinische Neurologie und Neurophysiologie† der Universität Freiburg, and Abteilung Neurologie der Medizinischen Fakultät der RWTH Aachen,‡ Federal Republic of Germany

SUMMARY In 15 patients with Huntington's disease, 17 offspring at risk and 63 healthy controls, visuomotor performances were assessed by quantitative (statistical) and qualitative analysis. The much enlarged error score of the nondominant left hand in patients with Huntington's disease was explained as callosal dyspraxia. Five of the 17 offspring revealed results similar to that of the patients.

About 75% of patients with Huntington's disease develop irregular motor signs either prior to or simultaneously with mental changes.¹ These motor symptoms are difficult to assess. Various attempts to measure these impairments have been focused mainly on the occurrence of abnormal involuntary movements during alternating motor tasks such as finger-tapping, rail-walking, placing pegs in a peg-board² or hand tremor recordings.^{1,3,4}

In the present study abnormalities observed during continuous voluntary visually-controlled movements were assessed. Since visual disturbances and atrophy of the occipital cortex are known to occur with Huntington's disease,^{5,6} the investigation of visuomotor coordination as a study of both the visual and motor performance seems especially suitable for establishing some of the characteristic abnormalities of Huntington's disease. A further purpose of the study was to detect subclinical abnormalities in clinically normal adult offspring of choreic families as a possible indication of incipient chorea.

Material and methods

Participating in the study were 15 patients with overt Huntington's disease and hyperkinetic involuntary movements, 17 healthy and clinically inconspicuous first generation

relatives of Huntington families and 63 normal controls. The mean age of the nine male and six female patients was 43.1 (± 12.5) years with an age range of 18 to 63 years; in offspring 30.8 (± 6.8) years with a range of 17 to 44 years; in normal controls 29.5 (± 10) years with a range of 20 to 66 years. The motor disturbance was slight in five patients, marked in seven and severe in three. One patient displayed the hypokinetic-hypertonic form of Huntington's disease, the other patients showing the more common hyperkinetic-hypotonic form. Progressive deterioration was obvious in all but two patients, every patient had a clear family history of Huntington's disease. The persons investigated were all right-handed. Handedness was confirmed by the Edinburgh handedness inventory.^{7,8}

All of the offspring in the study took part at their own request. Although the attempt at an early detection of an incurable disease such as Huntington's disease is a matter of controversy, the right of an individual to be fully informed of the information available and subsequently to be able to make a personal choice, cannot be ignored. With that as a prerequisite, a full discussion about the consequences and the uncertainties inherent in the procedure had taken place before the study began. Where the results turned out to be suspicious, the individuals received continuous supportive counselling.

The subjects had to solve 14 different continuous and discontinuous tasks (fig 1). Each task was carried out a total of four times: twice with the right hand, twice with the left; twice aiming for accuracy only, twice aiming for speed and accuracy. The number of errors was recorded for each of the 56 tasks ($14 \times 2 \times 2$) as was the time required for the solution. The sequence of testing conditions was the same for all subjects: starting with the dominant hand, the subject performed the task for accuracy only, then repeated it using the other hand. After that, copy papers were placed under the lines, the accuracy-plus-speed-instruction was given and the subjects started again with their dominant hand. Registration of the visuomotor performances was done with the following device (ZAK GmbH). A pen-

Address for reprint requests: PD Dr Godehard Oepen, Abteilung Allgemeine Psychiatrie der Universität Freiburg i. Br., Hauptstrasse 5, D-7800 Freiburg, Federal Republic of Germany

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Fig 1 The 14 tasks increasing in difficulty. Continuous tasks: 1-10 Discontinuous tasks: I-IV Original size of the pattern: 250 x 160 mm

cil with a light having a diode sensitive to reflected light was connected to an electronic device which counted the interruptions of the light signal. The subject was instructed to hold the pencil in a writing position and to draw along the black curves from a starting point to the end and reverse (fig 1). The patient's arm and hand were not supported on the table. When there was deviation from the black line on the sheet, a pin crossed a square grid, whereby the amount and duration of deviations was measured. The tracings were simultaneously copied onto copy paper. The complete test took about 1½ hours for the healthy subjects, about 2½ hours for the patients' group.

Results

Time and error performance totals for all 14 tasks were considered for the different conditions separately. These total scores are abbreviated as follows:

- R-S-T (right hand/slow/time)
- R-S-E (right hand/slow/errors)
- R-F-T (right hand/fast/time)
- R-F-E (right hand/fast/errors)
- L-S-T (left hand/slow/time)
- L-S-E (left hand/slow/errors)
- L-F-T (left hand/fast/time)
- L-F-E (left hand/fast/errors)

Table 1 gives the statistical description of the test performance of all three groups. In addition fig 2 shows the mean values (± 1 SD) for the three groups. Totalling T2 test and subsequent *t* test allowing for unequal variances, showed that the patients with Huntington's disease differ significantly from the control group in all variables but L-S-T and R-F-E, if Holm's⁹ sequentially rejective test procedure is used with an overall $\alpha = 0.05$; but the difference in the latter two variables is quite clear too. The time performance separates the two groups better than error performance (table 2).

The most striking result is displayed in the error performance of the left hand in Huntington's disease patients, which falls far above the expected range (fig 2).

To find out how well the performance in the eight variables (left/right x speeded/not-speeded x time needed/errors made) differentiated between the three groups investigated, a stepwise linear discriminant analysis was carried out (BMDP-program package)¹⁰ assuming equal prior probabilities. The

Table 1 Descriptive statistics for test performance of the three subject groups investigated: total time (T) and error (E) scores for the 14 visuomotor tasks given separately for each of the four experimental conditions both of the right (R) and left (L) hand and for slow (S) and fast (F) condition

	R-S-T	L-S-T	R-F-T	L-F-T	R-S-E	L-S-E	R-F-E	L-F-E
Controls (n = 63)								
$\bar{x}$	590.7	703.8	320.3	369.6	41.1	74.2	277.5	437.4
SD	137.2	123.9	46.7	58.4	46.7	69.8	173.5	223.4
Md	563	713	316	369	26	43	227	388
Max.	1131	950	479	512	228	290	893	1057
Min.	349	459	238	249	0	2	27	60
Offspring (n = 17)								
$\bar{x}$	673.5	778.9	393.7	438.1	57.6	115.8	268.4	471.3
SD	156.0	159.1	76.7	80.3	75.7	120.1	162.9	355.3
Md	653	772	362	416	31	63	238	390
Max.	1076	1220	575	666	317	389	586	1387
Min.	486	535	198	333	0	3	24	61
Huntington's disease (n = 15)								
$\bar{x}$	1124.8	1188.4	722.7	736.2	478.7	1235.2	783.9	1640.7
SD	448.0	471.6	276.3	269.2	399.7	1092.0	611.7	989.6
Md	989	1031	654	687	418	931	542	1379
Max.	1920	2038	1302	1302	1739	3678	2234	3780
Min.	587	611	452	424	72	264	76	178

Fig 2 Mean values of time (T) and error (E) Performance of offspring (± 1 SD), Patients with Huntington's disease and the control group [upper tolerance limit (± 2 SD) for healthy persons: $\star \cdots \star$]. Offspring $\circ \cdots \circ$ open circles, Patients $\bullet \cdots \bullet$ filled circles, Control group $+ \cdots +$ crosses.

variables R-F-T and L-F-E together were found to account for the separation between the three groups. In the discriminant analysis no member of the control group is classified as having Huntington's disease. No patient with overt Huntington's disease is classified as a member of the control group, the offspring are divided equally among the control and Huntington's disease groups. (Details of the jackknife classification, of the discriminant function values and canonical variables are available from the authors on request.)

The position of each individual subject and the means of the three subject groups can be depicted in a two-dimensional plot for the first two canonical variables (weighted linear combinations of those two variables separating best).

In fig 3 the mean value of the offspring group (No 3) falls between the mean values of the Huntington's disease patients (No 2) and the control group (No 1), but closer to the latter. The descrip-

tion of the individual subjects of the offspring groups shows five offspring (P) in the space between the mean value of the patient group (2) and the mean value of the offspring group (3). They also clearly outside the control group range. In table 1 the posterior probabilities are given, calculated with the aid of the classifying functions. The probability that each subject belonged to each group is presented. The above mentioned five conspicuous offspring are numbered 4, 5, 8, 10 and 14 (left to right in fig 3). Table 3b reveals that these are also the offspring having the highest posterior probability of belonging to the "at-risk" group. It is likely that these five offspring already have impaired visuomotor coordination.

The posterior probabilities for the 14 members of the control group classified as "at-risk" persons are between $p = 0.50$ and $p = 0.60$. This is due to the considerable overlapping of the control and the offspring groups, explained by the genetic fact that

Table 2 Observed significance levels for pairwise comparisons between subject groups (C = controls, O = offspring, HD = Huntington's disease). Differences between the test performance from *t* tests allowing for unequal variances (degrees of freedom corrected according to Welch) for the 8 total scores considered

p value	R-S-T	L-S-T	R-F-T	L-F-T	R-S-E	L-S-E	R-F-E	L-F-E
C-O	0.0584	0.0853	0.0012	0.0035	0.4011	0.1882	0.8410	0.7129
C-HD	0.0004	0.0014	0.0001	0.0001	0.0008	0.0010	0.0065	0.0003
O-HD	0.0017	0.0052	0.0004	0.0008	0.0011	0.0014	0.0061	0.0004

Fig 3 Two dimensional graphic description of all 95 subjects of the control group (N), offspring (P) and Huntington's disease patients (C) by the first two canonical variables. (The mean value of each group is indicated by numbers, details explained in the text).

50% of the offspring escape the disorder. The probability of belonging to the patients group is negligible for all 63 controls ($p = 0.00005$).
With respect to the posterior probabilities of the patients with Huntington's disease, it can be seen

that two of them are classified as members of the offspring group (patients No 8 and 13). These are the two patients (C) closest to the control and offspring group in fig 3. These two patients presented the shortest time of illness and only slight

Table 3 Posterior probabilities for allocation from the stepwise linear discriminant analysis (variables selected are R-F-T and L-F-E)

(a.)				(b.)			
Subject no.	A-posterior probability			Subject no.	A-posterior probability		
	Control	Chorea	Offspring		Control	Chorea	Offspring
1	0.000	1.000	0.000	1	0.489	0.000	0.511
2	0.000	1.000	0.000	2	0.485	0.000	0.515
3	0.000	1.000	0.000	3	0.505	0.000	0.495
4	0.001	0.977	0.021	4	0.251	0.001	0.747
5	0.000	1.000	0.000	5	0.192	0.213	0.595
6	0.000	1.000	0.000	6	0.640	0.000	0.360
7	0.000	1.000	0.000	7	0.641	0.000	0.359
8	0.239	0.000	0.761	8	0.279	0.004	0.717
9	0.000	1.000	0.000	9	0.444	0.000	0.556
10	0.000	1.000	0.000	10	0.267	0.000	0.733
11	0.000	0.998	0.002	11	0.517	0.000	0.483
12	0.002	0.980	0.018	12	0.558	0.000	0.442
13	0.164	0.018	0.818	13	0.532	0.000	0.468
14	0.000	1.000	0.000	14	0.348	0.000	0.652
15	0.000	1.000	0.000	15	0.387	0.000	0.613
				16	0.570	0.000	0.430
				17	0.590	0.000	0.410

(a.) Patients with overt Huntington's disease
(b.) Offspring.

Fig 4 Trace abnormalities in the tracking performance of a patient with Huntington's disease. The typical "lurches" and "darts" are indicated by arrows.

impairment as a result of the disease.

Offspring

The mean total time score for offspring is slightly above that of the controls but within the normal tolerance level. The mean error scores of the offsprings' right hand are nearly identical to those of the controls, the offsprings' error performance of the left hand is slightly worse, but not yet significantly (table 2). The difference between the mean time performances of the right and of the left hand in the offspring (fig 2) approximates that of the control group. Only the differences in the error

scores between the offspring's right and left hand seem to be larger. However, this difference is not as marked as in the Huntington's disease group.

Qualitative analysis of tracking performance

For qualitative analysis, the copy sheets of the continuous tasks 1–10 under the stress condition were used. The analysis of the choreic performance showed characteristic tracing abnormalities with typical "lurches" and "darts" (in fig 4 indicated by little arrows) and alterations in pencil pressure, which are not visible in the reproduction. All the patients showed these abnormalities; however, none of the controls did. The lurches and darts might be due to voluntarily suppressed hyperkinetic movements which must not be clinically detectable. So, several members of the offspring group showed similar qualitative abnormalities under the stress condition (fig 5). As can be seen in table 4, the five offspring (No 4, 5, 8, 10, 14) mentioned above show such abnormalities in a large portion of their tracing. Thus the results of the quantitative analysis correlate well with the qualitative analysis. For offspring No 2, 15, and 16 the tracing abnormalities do not correspond to the degree of posterior probability (table 3) and therefore they are not considered as conspicuous.

Discussion

Significance of time scores

The usefulness of measuring eye-hand-coordination

Table 4 Number of trials with typical "choreatic" abnormalities in Huntington's disease offspring during the continuous tracking tasks (figs 1 and 5).

Offspring	right hand	left hand
1	0	0
2	2	6
3	0	0
4	5	5
5	2	3
6	0	5
7	0	2
8	6	8
9	0	3
10	2	5
11	0	1
12	0	2
13	0	0
14	8	5
15	0	2
16	2	3
17	2	2

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Fig 5 Trace abnormalities of offspring No 8 with typical lurches and darts (indicated by arrows).

in Huntington's disease has already been mentioned.² The visual tracking task described above made it possible to record, detect and quantify the motor disturbance of patients with Huntington's disease.

From the motor behaviour in Huntington's disease with relatively undisturbed goal-directed movements, interrupted only by quick hyperkinetic movements, the error scores were expected to be high rather than the time scores. However, on the contrary, time scores were significantly higher than those of the normal controls and separated the groups better than the error scores (table 1), probably due to their smaller standard deviation. The unexpected accentuation of the time score might be further related to the increased reaction time associated with Huntington's disease,¹¹ the quantitative learning disorder,¹² the less systematic visual observation¹ and the disturbed eye movements and eye-head coordination.^{5, 13} Striking difficulties in performing visual tasks such as the Bender-Gestalt-Test,^{1, 12} reduced amplitudes in visual evoked potentials,¹⁴ myelin-loss in the occipital lobes,¹⁵ GABA-reduction in occipital white matter¹⁶ and cortical atrophy of the occipital pole in computed tomography⁶ support the assumption that Huntington's disease causes impairment of the visual system which further impair visuomotor coordination. In addition, isolated caudate lesions may lead to spatial motor deficits.¹⁷

From clinical observation, dysdiadochokinesis is known to occur in most Huntington's disease

patients. The investigation of H-reflexes¹⁸ also suggests a rather general motor disturbance with tonic disinhibition of spinal reflexes in addition to the phasic hyperkinesias. Our supplementary studies of motor and reflex behaviour have shown a general disturbance of agonist-antagonist innervation, which is not limited to the hyperkinetic jerks. This not only corresponds to the observation of slowness in the tracing tasks, but also to the inaccuracy of movement and the inability to maintain a rhythmical work tempo when directed to perform as rapidly as possible.¹

Evidence for callosal dyspraxia

The number of errors for the left hand was about three times worse than expected from the right hand performance (fig 2). This cannot be explained only by the different direction of right and left arm movement in each task, which in any case are reported to influence rapidity rather than accuracy.¹⁹ Also the unchanged sequence, in which the two arms were tested²⁰ seems not sufficient to explain the left hand disturbance, as it was never observed in patients with other neurological disorders (paper in preparation) nor in the other tested groups. The left hemisphere seems to exert a relative dominance over complex visuomotor functions, as is observed after brain lesions:²¹ sensorimotor coordination has been reported to be more impaired after left hemispheric lesions. In overt Huntington's disease, no focal hemispheric accentuation of the generalised degenerative process is known. Thus the above men-

tioned observation of accentuated sensorimotor left hand impairment might be due to a disorder of the transcallosal transfer. Similar observations in callosal apraxia have provided evidence for "a centre for visuo-kinesthetic (space-time) engrams in the left hemisphere of right handed patients, that controlled skilled motor acts in either hand".^{22,23} Furthermore the reported accentuation of disturbances of voluntary saccades compared to refixational saccades^{5,24} could also be interpreted as a disconnection syndrome.²⁵ This correlates with previously reported morphological alterations of the corpus callosum¹⁵ and confirms the suggestion of possible defective interhemispheric exchange in Huntington's disease.²⁶

Qualitative features

In addition to the quantitative measurements, the qualitative analysis which shows typical "lurches" and "darts" during continuous tracking that were never observed in normal subjects, also gives some diagnostic hint of Huntington's disease. Although these alterations are less pronounced in the conspicuous offspring, they are clearly visible and are characteristic for Huntington's disease. In patients with other neurological disorders of the motor system, such alterations were never observed (paper in preparation).

Offspring

The observation that some of the offspring group following the instruction "as fast and as accurately as possible" releases slight choreiform movements which are less apparent during relaxation, is of special interest for early detection. Again, this tendency is often more obvious in the left hand. By means of a linear discriminant analysis, the offspring group could be classified according to their performance into two subgroups: one made up of the controls, the other of those who with substantial probability are already affected by the disease. This division was reinforced by the qualitative analysis of the subjects' subtest performances, which showed the same abnormalities that could be seen in subtest tracings of patients with Huntington's disease.

For early detection the visuomotor test we have described should be applied in combination with other tests to improve the probability of detecting minimal chorea.²⁷

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