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Reaction time and rhythm of movement in Huntington's disease

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ABSTRACT

Huntington disease (HD) is characterized by several hyperkinesias though motor slowness is also another cardinal in this disease. In addition, self-paced timing movements are also disturbed in HD, which may also affect several rhythmic voluntary movements such as gait. Motor slowness can be measured with clinical scales such as the Unified Huntington's Disease Rating Scale (UHDRS) and timed tests, but also with the reaction time (RT) paradigm.

We evaluated RT as a measure of motor slowness in 30 patients with genetically confirmed Huntington's disease and 24 control subjects. We also evaluated self-paced timing precision (SPTP) by applying a simple software program devised by our group. Clinical assessment was performed according to the UHDRS, including motor section, total functional capacity (TFC) and cognitive section (verbal fluency test, symbol digit, and Stroop test)

The mean values obtained for RT and SPTP were statistically different in HD as compared with those from controls ($p < 0.0005$). We observed a statistically significant correlation between RT and TFC scores ($rs = -0.57$, $p < 0.005$ Spearman's correlation) and also between SPTP values and TFC scores ($rs = -0.40$, $p < 0.05$ Spearman's correlation). In addition, RT and SPTP significantly correlated with cognitive scores (including digit symbol, verbal fluency and Stroop tests).

Simple tests such as RT and SPTP provide an objective evaluation of motor impairment in HD yielding measures that correlate with clinical assessment and functional disability.

1. Introduction

Huntington's disease (HD) is a progressive neurodegenerative disorder related to CAG trinucleotide repeat expansion [1]. Clinically, HD is characterized by abnormal movements, cognitive decline and psychiatric disturbance [2]. Motor disorders are heterogeneous in HD and several hyperkinesias (including chorea, tics and dystonia) can coexist with an akinetic–rigid syndrome characterized by motor slowness that includes slow initiation of movement (akinesia) and slow movement (bradykinesia) [3–5]. Motor slowness occurs with increasing severity over time in HD [4–7], but can be detected early in the course of the disease, even in presymptomatic individuals [8–11]. Actually, functional disability in HD is associated with impairment of voluntary movements rather than chorea [12–14].

In clinical practice, motor slowness is measured with clinical scales such as Unified Huntington's Rating Scale (UHDRS) [15]; timed motor tests [16] and by neurophysiological methods [17], including ambulatory monitoring and the reaction time (RT) paradigm [11,18]. Neuropathological studies in HD demonstrated neuronal loss in the striatum and the clinical phenotype depends on the disruption of motor cortico-striatal circuits [19]. Striatal lesions play an important role in impairment of reaction time [20].

In addition to motor slowness, motor irregularity is evident in HD; impaired self-paced timing precision (SPTP) is also present in this disease, which probably explains in part, the irregular and poorly coordinated gait that is characteristic of HD [21].

The main objective of this study is to assess the motor performance of HD patients by means of RT and SPTP and correlate these measures with clinical evaluation.

2. Subjects and methods

All patients were recruited from the outpatient clinic of the movement disorders unit at our center. Thirty genetically confirmed HD patients (age: 47.0 ± 11 years; duration of the disease: 7.4 ± 4.8 years; CAG expansion: 45.6 ± 5.3; UHDRS total mean score: 41.2 ± 22) and 24 normal subjects of similar age (43 ± 20 years) were included. All patients were evaluated clinically with UHDRS (15); including motor section, TFC and cognitive section. We analyzed the bradykinetic–rigid items and choreatic items of the UHDRS motor section separately (14).

The experimental tasks were as follows:

– Reaction time (RT): Response latency was measured with the use of a software program designed for the purpose of this study; the patient or control was instructed to sit 1 meter away from the

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computer screen and was told to respond as quickly as possible to the appearance of random visual stimuli (red square 6 cm × 6 cm) on the corner of the screen by pressing a key (space bar). The visual stimulus appeared 20 times on the screen at random.

– Self paced timing movements or rhythm of movement (SPTP): Patients or controls were instructed to produce a constant rhythm by pressing a key on the computer (space bar). The program measured the consecutive time between keystrokes as well as the standard deviation. This test allowed for accurate measurement of rhythm (higher values denote lower degrees of rhythm, and lower values for standard deviation express more rhythmic tapping). The test concluded when the patient or control had produced 40 keystrokes. All patients and controls were previously trained before the experiment.

The RT and SPTP mean values between HD patients and controls were compared with Student t test. Correlation between RT / SPTP and clinical variables were studied with Spearman's correlation coefficient (for non-parametric variables) or Pearson's correlation (parametric variables).

An informed written consent was obtained from each patient and control. The local ethics committee approved this work.

3. Results

We found statistically significant differences in mean RT values between HD patients and control subjects. Patients with HD had much higher RT compared with controls (419.9 ± 113 ms vs. 294.2 ± 29 ms, $p < 0.0001$ Student t test).

SPTP was also found to be disturbed in HD. Significant differences were also observed in SPTP mean values between HD patients and controls. Patients with HD had a poor capacity of self-paced rhythm control compared with control group (237.4 ± 113 ms vs. 146.7 ± 20 ms, $p < 0.0001$ Student t test). Table 1 summarizes the global motor and cognitive results.

As only 4 patients were receiving neuroleptics, we also calculated the results by ruling out those 4 patients; the results were quite similar (RT and SPTP for HD without neuroleptics versus control were respectively: 405.6 ± 108 ms vs 294 ± 29 ms, $p < 0.0001$ Student t test; and 239.5 ± 116 ms vs 146.2 ± 20 ms, $p < 0.0005$ Student t test).

The HD group exhibited higher standard deviation in SPTP values as compared with controls, these differences were significant. These results may reflect variability and irregularity in the degree of rhythm of self-paced movements.

Table 1
Global results.

	HD group (30)	Control group (24)
Age at onset	40 ± 11.05	
Evolution in ys	7.4 ± 4.8	
Present age	47.0 ± 11	43.04 ± 20
(CAG) expansion	45.6 ± 5.3	
UHDRS total score	41.2 ± 22.3	
UHDRS hypokinesia–rigidity	9.4 ± 5.4	
UHDRS Chorea	11.20 ± 7.2	
Total functional capacity	9.1 ± 3.1	
Verbal fluency	26.9 ± 8.8	
Digit symbol	29.1 ± 10.3	
Stroop color	45.8 ± 15.3	
Stroop word	64.7 ± 25.2	
Stroop interference	29.2 ± 10.4	
Reaction Time (ms)	419 ± 113.6	294.2 ± 29
Self-paced timing (ms)	237.9 ± 113.8	146.7 ± 20.8

Note: data are mean ± standard deviation.

Table 2
Reaction time (RT) and self-paced timing precision (SPTP) correlation.

	RT	SPTP
Age at onset	N.S.	N.S.
Evolution in ys	**r: 0.48 p < 0.01**	N.S.
Present age	N.S.	N.S.
(CAG) expansion	N.S.	N.S.
UHDRS total score	**r: 0.38 p < 0.05**	**r: 0.40 p < 0.05**
UHDRS bradikinesia–rigidity	**r: 0.41 p < 0.05**	**r: 0.51 p < 0.005**
UHDRS chorea	N.S	N.S.
Total functional capacity	**r: −0.57 p < 0.005**	**r: −0.40 p < 0.05**
Verbal fluency	**r: −0.40 p < 0.05**	**r: −0.50 p < 0.005**
Digit symbol	**r: −0.61 p < 0.0005**	**r: −0.65 p < 0.0001**
Stroop color	**r: −0.61 p < 0.0005**	N.S.
Stroop word	**r: −0.47 p < 0.01**	**r: −0.40 p < 0.05**
Stroop interference	**r: −0.55 p < 0.005**	**r: −0.45 p < 0.05**

Bold values indicates statistical significance level: $p < 0.05$.

RT and SPTP mean values correlated with total and bradykinesia–rigidity UHDRS scores (Table 2). In addition RT clearly correlated with TFC (Fig. 1).

Finally, RT and SPTP correlated with cognitive tests, including Stroop tests. Neither RT nor SPTP correlated with (CAG) length, age at onset or present age, but TR correlated with evolution in years ($p < 0.05$). Table 2 summarizes the RT and SPTP correlation with motor, TFC and cognitive scores.

4. Discussion

Slowness of movement is a cardinal feature in HD [3–13]. Slowness of movement, as measured by RT was clearly present in HD patients. Previous studies have suggested that impairment of voluntary movements correlates with functional disability [5,6]. In addition, slowness of movements is not only present in advanced HD but also early in the course of the disease [9–11], indeed 60% of our patients had a relatively mild disease and were independent for activities of daily living. A minority of our patients were treated with neuroleptics, although the influence of neuroleptics in the experimental motor tasks seems to be irrelevant, since ruling out the measures of those patients taking neuroleptics from the rest did not influence the overall results. In any case, the dose of neuroleptics (olanzapine, quetiapine) was a low one in each case.

It seems that bradykinesia and akinesia, as suggested previously are cardinal symptom in HD [4,5,14,17]; the reason for this is debated, according to Berardelli et al. The coexisting hyperkinetic and hypokinetic movement disorders probably reflect the involvement of direct and indirect pathways in the basal ganglia–thalamus–cortical motor circuit (17).

RT as a "objective" measure of motor slowness correlates with clinical scales and functional disability. In addition, rhythm generation seems to be clearly affected in HD; SPTP is impaired in HD, and this can partly explain, the classical irregular gait pattern that is so typical of HD [21].

In our patients, RT and SPTP also correlated with cognitive deterioration, at least with several tests including verbal fluency, digit symbol, and Stroop color.

Recently, Antoniades et al. studied the inter-tap interval in HD patients with a refined tapping test paradigm [22], in this interesting paper, differences in the finger tapping data related to HD severity as measured by conventional behavioural tests [22].

In summary, it seems that objective markers of slowness of movement are useful in the evaluation and follow-up of HD [3–5,12,13,17,22]. Neuroprotective drugs are badly needed in neurodegenerative diseases such as HD, but to confirm the neuroprotective effect of any given therapy, an accurate and reproducible evaluation is clearly advantageous. In this regard simple, inexpensive measures such as timed tests