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ORIGINAL COMMUNICATION

Hand tapping: A simple, reproducible, objective marker of motor dysfunction in Huntington's disease

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Abstract Huntington's disease (HD) is a severe neurodegenerative condition in which the impairment in voluntary movement is related to functional disability. Clinical assessment of motor deficit currently relies largely on subjective rating scales without objective measurement. We have developed a quick and easy-to-use hand tapping device that enables measurement of (a) the number of taps in 30 seconds, (b) variability in tapping rhythm and (c) fatigue over the testing period. Initial cross-sectional testing of 178 consecutive HD clinic patients using an early model of the device showed that the total number of taps in 30 seconds correlated with the motor UHDRS (Spearmann's rho, $r_s = -0.81$, $p < 0.0001$) and independence scores ($r_s = 0.78$, $p = 0.01$). Longitudinal data from a small cohort followed over 10 years reveals a correlation between total number of taps in 30 seconds and motor UHDRS over time ($r_s = -0.49$, $p < 0.001$), and suggests the technique may provide an objective measure of disease progression. Further tests on 15 HD patients and 9 controls were repeated three times in a single day using an updated device. The HD group made significantly fewer taps in 30 seconds (median HD = 79, control = 104, $p = 0.009$) and had greater variability of inter-tap interval (mean interdecile range HD = 148, control = 56, $p = 0.016$) compared to controls. Both the total number of taps and variability of inter-tap interval correlated with motor UHDRS. Of vital importance for any potential marker of disease progression is that these tapping parameters were reproducible with repeated measurement. Given that hand tapping parameters differ between HD and control populations, they correlate with motor UHDRS over time and are reproducible, we propose that assessment of hand tapping represents a useful objective adjunct to the clinical assessment of HD patients.

Key words Huntington disease · biomarker · hand tapping

Introduction

Huntington's disease (HD) is a progressive neurodegenerative condition caused by an expanded CAG trinucleotide repeat in the HD gene on chromosome 4 [1]. Although the number of CAG repeats correlates with the age of symptom onset this remains difficult to predict [5]. Furthermore, the correlation between number of CAG repeats and disease progression is imprecise [16]. Once clinically apparent the disease relentlessly progresses, albeit in an unpredictable manner, until death occurs approximately 15–20 years after symptom onset.

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Over the past decade a number of potential neuroprotective treatments have been investigated, with some evidence of beneficial effect in transgenic animal models of HD [11]. Of course new treatments must ultimately be tested in the human disease, where they must be shown both to alter the progression of pathology over time and to retard the clinical progression of the disease. To this end there is a great need for sensitive, reproducible biomarkers of HD which are able to objectively follow disease progression and detect treatment effects.

Although the ultimate aim of treatment is clinical (and correspondingly, the ultimate aim of a treatment trial is to prove that an intervention slows clinical progression), the clinical phenotype is difficult to assess objectively. At present the most commonly used approach is to sum a number of structured subjective clinical observations to generate a score on a rating scale such as the Unified Huntington's Disease Rating Scale [2] or the Quantified Neurological Examination [6]. Whilst the benefit of clinical examination lies in its breadth and ability to detect a wide variety of deficits, its weakness lies in its subjectivity, rendering it susceptible to variation, albeit relatively mild, depending on the assessing physician [2]. There remains, therefore, a need for a simple, inexpensive and quick objective measurement of clinical phenotype to supplement standard clinical assessment.

The movement disorder experienced by patients with HD is complex, comprising not only chorea, but also a general poverty of movement that includes a delay in movement onset (akinesia), slowing of movement (bradykinesia), reduced movement throughout the day (hypokinesia) and inaccuracies in the force and trajectory of movements once executed (see for example Quinn et al. [14]). Although it is impossible to measure quickly all aspects of the movement abnormality, there are a number of strands of evidence that suggest that an objective measure of voluntary movement might represent a good marker of clinical disease severity throughout the course of HD. Firstly it seems that the impairment in voluntary movement is closely related to the functional disability experienced by patients [2, 7, 20, 21], suggesting that a faithful marker of the movement abnormality may also reveal functional status. Secondly, motor deficits can be detected early in the disease process, even in presymptomatic gene-positive subjects [8, 9, 19], raising the possibility that an objective marker might be of use even in early disease. And finally, motor deficits progress in line with other clinical measures of disease stage [17, 20, 21], and correlate with the loss of striatal D2 binding on raclopride 11C PET [18]. Such observations suggest that objective measures of motor function may indeed change over time, allowing us to follow disease progression.

A small number of studies have addressed the quantitative assessment of motor phenotype in HD [3, 4, 7, 8, 15, 17, 20, 21]. Of particular note, Garcia Ruiz and colleagues [7] found a difference between HD and control populations using the four motor tests suggested in the CAPIT [10]. They found that the assessment of hand tapping between two points 30-cm apart correlated with total functional capacity and UHDRS motor score. Furthermore, they found some evidence for change over time with disease progression. Van Vugt and colleagues used a different approach and measured both the reaction time and movement time to a button 6.5 cm away. They confirmed that objective measures correlated with clinical rating scale and changed concomitantly over time [20]. Finally, Saft and colleagues have recently identified a correlation between a subject's ability to tap a single target (maximum number of taps in 32 seconds) and caudate atrophy, CAG index (number of excess CAG repeats multiplied by the age of the patient) and UHDRS score [17]. Furthermore they have recently shown evidence that their test results correlate with the deterioration in UHDRS score in 42 patients followed over 3 years [3].

Any system designed to monitor HD motor phenotype objectively in the clinic must be simple and quick to use, and ideally require no special training. We designed a device to assess hand movement based on the tapping test described in the CAPIT [10]. It consists of two buttons spaced 30 cm apart that have to be depressed alternately as rapidly as possible for 30 seconds. Given the promising results obtained from the initial device a second system was built which incorporated a timing system to allow objective assessment of variability of inter-tap interval and fatigue during the testing period.

The objective of this study was not to replace the clinical/UHDRS assessment, but to supplement it with an easily used objective measure of motor deficit. By comparing the hand tapping device in HD patients and controls we aimed to answer four key questions: i) whether the hand tapping device was able to detect a difference between HD and control subjects, ii) whether the severity of deficit correlated with the severity of clinical phenotype assessed with current rating scales, iii) how this relationship changed over time, and finally, but crucially, iv) whether tapping scores were reproducible. The rationale for using these four conditions was that they represent the minimum requirement of a device that might be useful as an adjunct to standard clinical assessment in longitudinal studies. This has important implications for trials of disease modifying therapy, potentially enabling quick and accurate quantification of any treatment effects.

Methods

All patients were recruited from the regional HD clinic at the Cambridge Centre for Brain Repair and had genetically proven disease.

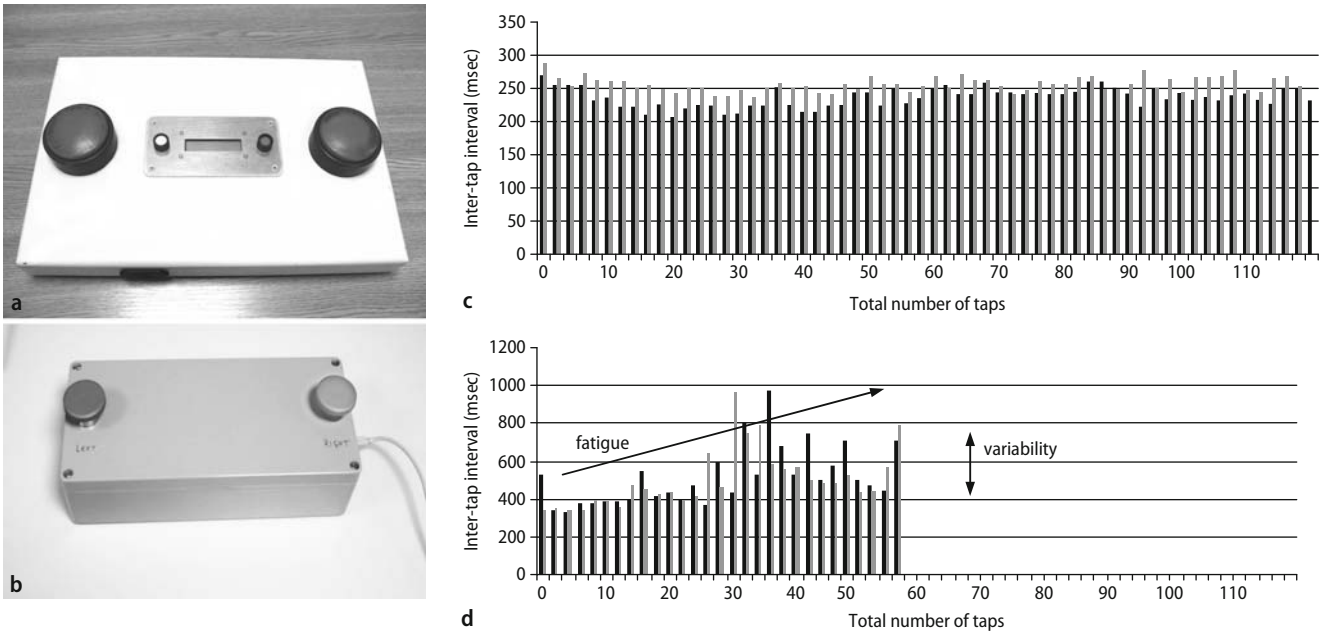

Fig. 1 Measurement of number of taps and inter-tap interval. The original hand tapping device (**a**), with which the total number of taps in 30 seconds was recorded, but not inter-tap interval. **b** The updated hand tapping device used to record inter-tap interval as well as total number of taps. Distance between the buttons remains the same as the original device. **c** Example results from a control subject (total number of taps = 119; fatigue, % decrement = 7.3; variability, IDR = 47, age = 46). **d** Example results from a subject with HD (total number of taps = 58; fatigue, % decrement = 15; variability, IDR = 405; age = 78; motor UHDRS = 42; independence score = 75). (Black bars depict inter-tap interval for right to left movement; grey bars for left to right movement; fatiguability: % decrement in number of taps; variability of inter-tap interval: inter-decile range, IDR. See Methods for further details)

Control subjects with no known neurological disease were recruited from friends or relatives accompanying patients to clinic.

The original hand-tapping device (Fig. 1a) was designed as a simple objective measure of motor function for use in the assessment of patients in clinic. It consists of two buttons 6 cm in diameter, mounted with their centres 30 cm apart. The subject's task was to alternately tap one button after the other as rapidly as possible using the palm of the right hand. Accuracy was not assessed. The total number of taps made in 30 seconds was recorded twice, and the mean value calculated.

The original device was used to collect data from 178 consecutive patients, 54 of whom were taking no medication, from November 2003 to October 2005. In addition longitudinal data over 10 years were available from a subgroup of 17 patients in whom hand tapping assessment was combined with UHDRS motor assessment as well as measures of functional capacity and an independence score. Since the initial visit of these patients was not simultaneous, the duration of their follow-up to date varies, thus 10 year follow-up data are not available for all patients. This does not reflect patient attrition (at 9 years follow-up n = 9 for tapping data and n = 10 for UHDRS, whereas at 10 years n = 3 and 8, respectively). Data were collected with both hands, and the longitudinal study presents the mean of left and right scores. Since data were almost identical, only right hand data are shown in cross-sectional work. Original data for the first couple of years were collected manually before the first, and subsequently second, tapping device was available (distance between the tapping targets, or buttons, remained identical throughout, as did test duration).

Following the promising results obtained with this device an updated version of the tapping device was built (Fig. 1b) with an identical distance between left and right buttons to the original. The device consisted of a simple timing circuit triggered by initial button depression, and which subsequently logged the time of every button depression for 30 seconds. This information was downloaded real-time to a Microsoft Excel spreadsheet run on a laptop computer, where the inter-tap interval and total number of taps was automatically calculated. The electronic circuit was housed in a strong steel case. Total cost of development and production of this device was approximately £400 (US$ 800, € 700), but the machine could easily be produced in bulk, reducing this cost.

Automated measurements of inter-tap interval were examined on the computer screen whilst the patient performed the tapping test to ensure that any malfunction of tap detection was picked up. Approximately 2 % of taps were not detected due to inadequate pressure on the buttons. These errors were easily detected and deleted because the intertap interval was excessively long. Using this machine 15 HD subjects and 9 controls were tested on 3 occasions (morning, lunch and afternoon) in a single day to allow assessment of reproducibility.

Data analysis

Examples of the raw inter-tap interval data for a control and HD subject are presented in figure 1c,d. From these raw data three parameters were determined:

Number of taps Total number of taps in 30 seconds.

Fatigue (percentage decrement in number of taps) A measure of the percentage reduction in the rate of tapping over 30 seconds. % decrement = [(no. taps in 1st 10 s) – (no. taps in 3rd 10 s)]/(no. taps in 1st 10 s) × 100.

Variability (inter-decile range, IDR, of inter-tap interval) A measure of the spread of inter-tap intervals over 30 seconds excluding the small number of outliers, some of which represented a failure of detection or insufficient button depression. Since the distribution of inter-tap intervals was skewed, the interdecile range (IDR) was used instead of the variance. At each time point: variability = interdecile range from 10th to 90th centiles.

Each of the above parameters was determined at three points during the day, and the mean of these three recordings was taken in order to compare control with HD patients, and to correlate with motor UHDRS score. Comparison of the mean value of these three non-Gaussian distributed parameters in HD versus control groups was made with the Mann-Whitney U test. Correlation between mean tapping parameters and either motor UHDRS or independence score was performed with Spearman's rank correlation coefficient (r_s).

An assessment of the reproducibility of tapping measures across the three trials was performed by calculating three different parameters, each of which provides different yet complimentary reproducibility measures. Firstly, mean inter-trial correlations were calculated. Secondly, Cronbach's alpha was used, which compares the between-subjects variability to that within-subjects. Finally, Lin's coefficient of concordance was calculated [12, 13] since it incorporates a measure of the precision of reproducibility (Pearson r value) along with changes in the slope and y-intercept of the regression line from their expected values (slope = 1, y-intercept = 0), and is thus a more stringent test of reproducibility. For all three measures, values close to 1 suggest good reproducibility.

Results were considered statistically significant if $p < 0.05$.

Results

The mean age of the 15 HD patients assessed using the updated tapping device was 58.1 years (range 43–78), mean motor UHDRS score 25 (range 0–62) and mean disease duration 5.8 years (measured from onset of symptoms, range 0–14). Four were on no medication at all. Mean control age was 55.2 years (range 34–77). The mean age of the 178 HD patients assessed using the older tapping device was 49.9 years (range 15–81), mean motor UHDRS score 29 (range 0–83) and disease duration 4.7 years (range 0–15). 54 of these patients were receiving no medication. The longitudinal group contained 17 HD patients who, at latest assessment, had a mean age of 54.4 years (range 41–70), symptomatic disease duration of 13.2 years (range 1–20) and motor UHDRS score of 40.1 (range 13–87).

The total number of taps in 30 seconds measured with the original device significantly correlated with the motor UHDRS score ($r_s = -0.81$, $p < 0.0001$; Fig. 2a) and independence score ($r_s = 0.78$, $p = 0.01$; Fig. 2b) in the original large cross-sectional study of patients (n = 178) from the HD clinic. Since this population included some patients who were asymptomatic and had no signs, the calculations were repeated after removing subjects with a motor UHDRS < 5, or independence score (IS) of 100 %. In both cases the correlation with total number of taps remained highly significant (motor UHDRS: $r_s = -0.77$, $p = 0.01$; IS: $r_s = 0.65$, $p = 0.01$).

When followed longitudinally over several years the total number of taps in 30 seconds decreased, and motor UHDRS scores showed disease progression (Fig. 3). A correlation was found between motor UHDRS and number of taps over time (mean Spearman correlation between tapping and motor UHDRS, r = –0.49 (95 % CI = –0.63 to –0.34), $p < 0.001$). The increase in SEM error bars over time occurs in part because not all patients have been assessed to 10 years since their initial assessments were staggered.

The updated tapping device capable of measuring each inter-tap interval is shown in Fig. 1b, along with a typical example of the raw HD and control results after download directly to a laptop computer. In comparison to the control subject, the HD patient was not able to make as many taps in 30 seconds (with corresponding prolongation of the time between taps) and tended to fatigue towards the end of the 30 second recording period (shown by the increase in inter-tap interval). Furthermore, there was greater variability in duration of inter-tap interval throughout the recording period.

As a group, HD subjects made significantly fewer taps in 30 seconds and had increased variability of inter-tap interval (mean inter-decile range, IDR) compared to controls (Fig. 4 and Table 1). However, fatiguability (mean percentage decrement) was not significantly different between the two groups. For all three parameters the ranges of the control and HD populations over-

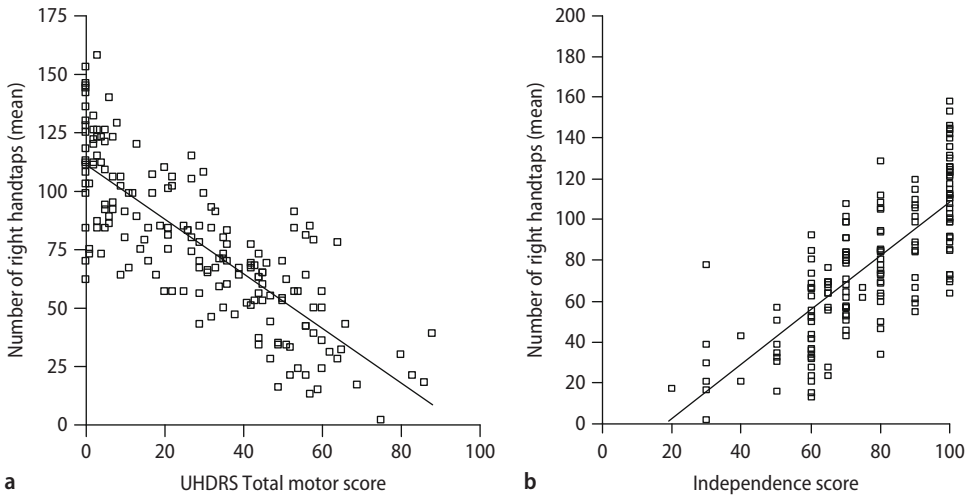

Fig. 2 Hand tapping correlates with clinical assessment. Total number of right hand taps (mean of two trials) correlates with motor UHDRS (**a**), and independence score (**b**), in a large population (n = 178)

lapped, as exemplified in Fig. 4a for the total number of taps. Nevertheless, total motor UHDRS correlated well with both the mean total number of taps ($r_s = -0.817$, $p < 0.001$) and mean IDR ($r_s = 0.844$, $p < 0.001$, Fig. 5), but not with mean % decrement ($r_s = 0.365$, $p = 0.18$).

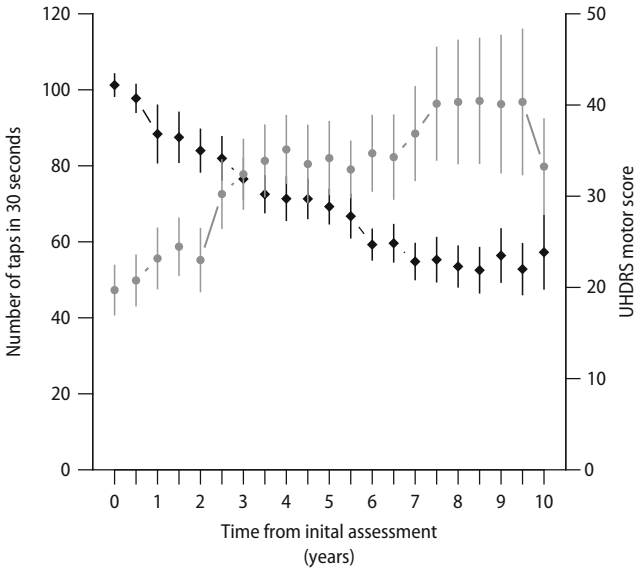

Fig. 3 Correlation of number of taps in 30 seconds with motor UHDRS over time. For individuals the mean of left and right hand tapping scores were calculated. Grouped annual tapping scores and motor UHDRS (mean ± SEM) are plotted against time from the individual's initial hand tapping measurement. N = 17 patients for early time points, but is less at 9 and 10 years (see text) since patients were initially assessed at different time points, so have not all been followed up for equal time periods. (Filled circles and thick grey error bars depict motor UHDRS data)

Table 1 Statistical comparison of tapping parameters between 15 HD and 9 control subjects. For each patient the mean of the three recordings made in a single day was taken for each tapping parameter (number of taps, fatigue and variability). Values presented are the population (control or Huntington's disease) median and interdecile ranges for these mean (individual) values of each parameter. P values shown are those without removal of outliers, but significance was unchanged with outliers removed (as displayed in Fig. 4)

	Control (n = 9) Median (IDR)	HD (n = 15) Median (IDR)	Mann-Whitney z	p value
Mean no. of taps in 30 seconds	104 (84 to 122)	79 (18 to 111)	−2.59	< 0.01
Mean fatigue (% decrement)	−2.7 (−11.5 to 9.1)	1.4 (−20.8 to 32.6)	−1.64	0.1
Mean variability (IDR)	56 (28 to 82)	148 (41 to 2343)	−2.41	< 0.02

fatigue % decrement in number of taps over 30 seconds; *variability* inter-decile range; *IDR* of inter-tap interval. See methods for further details

Both the total number of taps in 30 seconds and the variability of inter-tap interval (IDR) parameters were reproducible when measured on three occasions throughout a single day. This is shown graphically in Fig. 6a, and was confirmed with measures of reproducibility: inter-trial correlations, Cronbach alpha and concordance scores (Table 2). Note that Cronbach's alpha provides a number that reflects the ratio of variance between subjects compared to that within subjects. There-

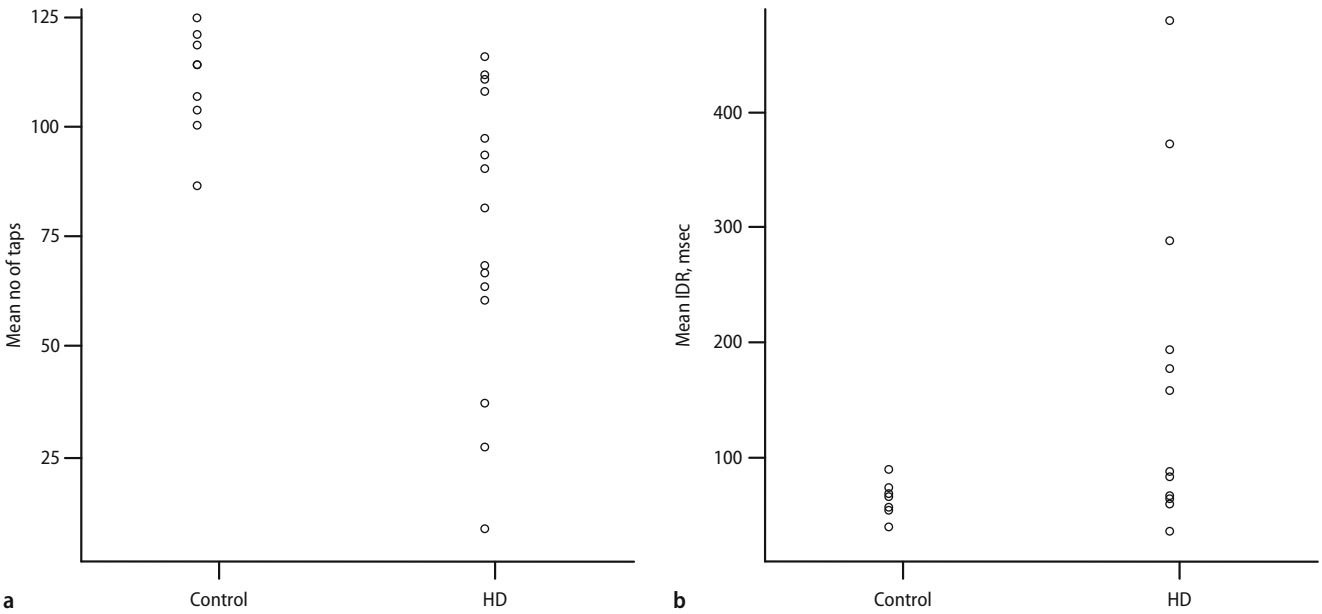

Fig. 4 Comparison of tapping parameters between 15 HD and 9 control subjects. Mean number of taps are greater in control subjects than HD patients (**a**). In (**b**) two HD patients with variability (mean IDR) much greater than 500 ms have been excluded for clarity of presentation. No subjects were excluded for the statistical analysis (presented in Table 2), and significance was not affected by presence or absence of outliers (fatiguability: % decrement in number of taps over 30 seconds; variability of inter-tap interval: inter-decile range, IDR. See Methods for further details). There was no difference in fatigue (mean % decrement) between the groups (not shown)

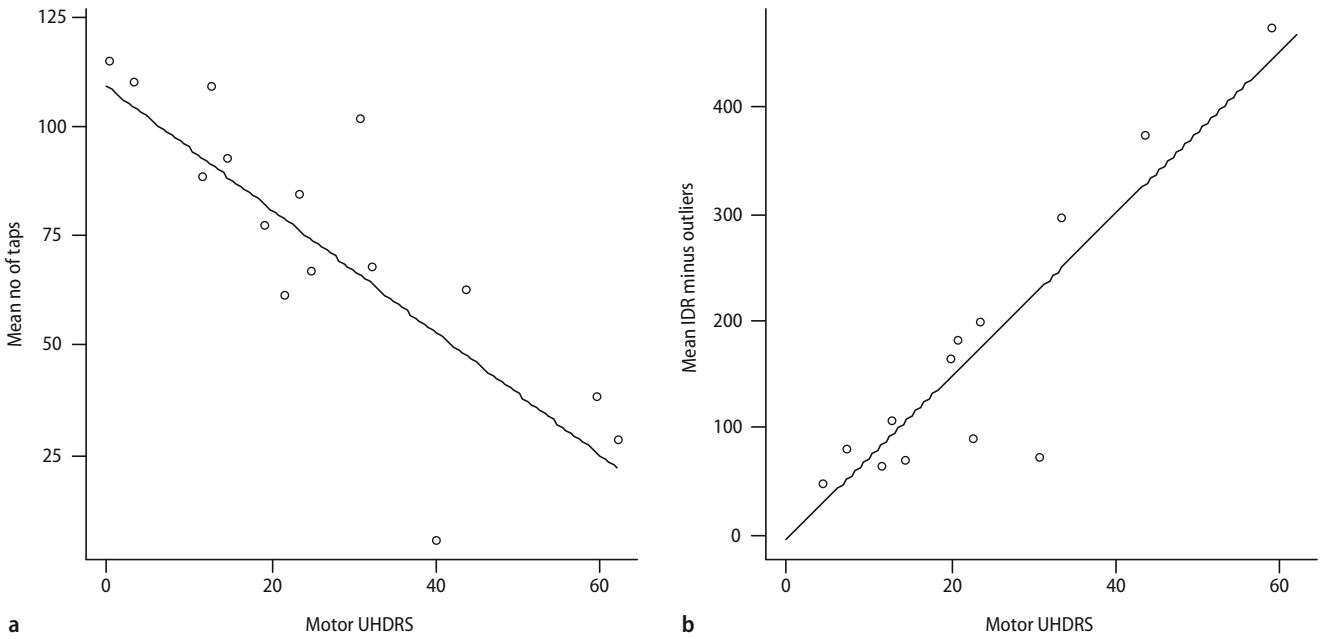

Fig. 5 Hand tapping scores correlate with clinical assessment. Two tapping parameters correlate well with motor UHDRS score: total number of taps (**a** $r_s = -0.817$, $p < 0.001$), and variability (interdecile range, IDR, 5b: $r_s = 0.844$, $p < 0.001$). The mean of the three trials in a single day has been taken for each patient. Graph **b** shows data minus two outliers in whom the mean IDR was much greater than 500 ms in order to improve clarity, however significant correlations exist both with and without these outliers (figures in the text include all data). Regression lines fitted

Table 2 Reproducibility of the three tapping parameters. Both the measurement of total number of taps in 30 seconds and the variability of inter-tap interval (interdecile range, IDR) are reproducible when measured on three occasions throughout a single day. This is confirmed with concordance scores (after Lin 1989, 2000 [12, 13]), Chronbach alpha and mean inter-trial correlation scores all close to 1

	Mean inter-trial correlation	Cronbach alpha	Concordance	
			am-noon	noon-pm
Number of taps				
Control	0.67	0.86	0.42	0.84
HD	0.92	0.97	0.90	0.96
Combined	**0.91**	**0.96**	**0.83**	**0.96**
Fatigue (% decrement)				
Control	0.07	0.40	0.12	0.51
HD	0.21	0.48	0.10	0.02
Combined	**0.24**	**0.50**	**0.11**	**0.16**
Variability (IDR)				
Control	0.56	0.74	0.70	0.41
HD	0.83	0.89	0.96	0.69
Combined	**0.86**	**0.91**	**0.97**	**0.74**

fore a value close to 1 suggests good within-subject reproducibility, in comparison to the variance between subjects. In Table 2, for example, HD subjects have a Cronbach's alpha score for the total number of taps that is closer to 1 than controls because the latter have less between-subject variability. It is for this reason that in order to assess reproducibility the data are presented graphically (Fig. 6). The mean inter-trial (Pearson) correlation is a commonly used estimate of the correlation between different trials, but only measures the spread of data points around the regression line (precision) and would not detect whether, for example, subjects made twice as many taps in the evening compared to lunch. The concordance correlation coefficient takes this into account and the high value obtained for the number of taps (0.96) indicates excellent reproducibility.

Of note there seems to be a slight learning effect evident if one compares total number of taps recorded at noon to the morning ($t = -3.91$, $df = 21$, $p = 0.001$), but no further improvement between noon and afternoon scores ($t = -1.23$, $df = 21$, $p = 0.23$). This is evident in Fig. 6a and is also shown by the slightly better concordance values between noon and afternoon scores than morning and noon values (Table 2). This does not seem to affect percentage decrement or variability scores.

Conclusions

The objective assessment of motor function in patients with HD is easily and rapidly achieved by using a hand tapping device that enables testing and storage of results within approximately 1 minute. Using an original device, without inter-tap timing, we have shown that the total number of taps in 30 seconds correlates well with motor UHDRS and independence score. Furthermore, the relationship persists in a prolonged longitudinal

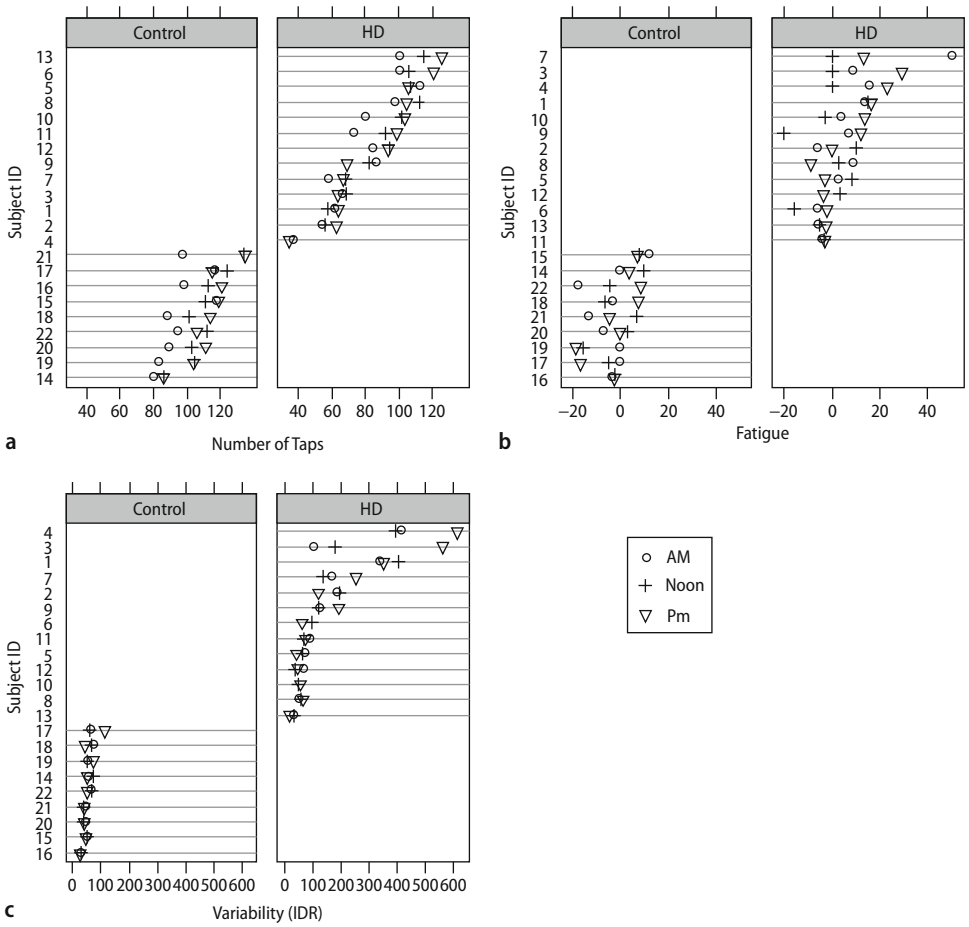

Fig. 6 Hand tapping parameters are reproducible when remeasured. Total number of taps, fatigue (% decrement in number of taps) and variability (interdecile range, IDR, of the intertap interval) are plotted throughout the day for each subject in order to examine reproducibility. Note that total number of taps (**a**) and IDR (**c**) appear to be more reproducible measures than % decrement (**b**). Subjects are grouped according to genotype and have been ranked according to highest value of each tapping parameter

study, with total number of taps in 30 seconds correlating to UHDRS over time. A second more sophisticated device enabled measurement of inter-tap interval in order to quantify the fatigue and variability of inter-tap interval subjectively noticed when HD subjects used the original hand tapping device. Using this updated device we have shown that the HD population make a significantly reduced number of taps in 30 seconds and have greater variability of inter-tap interval than controls. The observation that the control and HD ranges overlap means that the test could not be used to assist diagnosis (a role that is fulfilled by genetic testing), but it does not rule out use of the device to follow disease progression and possibly even predict symptom onset.

Importantly we have found that both the total number of taps and variability of inter-tap interval correlate well with motor UHDRS. Furthermore, and again of vital importance for any potential marker of disease progression, we have shown that these two tapping parameters are reproducible if repeated measures are taken. Given there is a slight learning effect, with a small improvement in total number of taps between first and second testing sessions, it may be best to perform two recording trials and use results from the second trial only. In addition a good case can be made for allowing subjects to tap with their dominant hand. In this instance the right hand was chosen for continuity with our previous work.

The most useful role for biomarkers of HD clinical phenotype would be to follow disease progression objectively over time, and the current longitudinal study provides evidence to suggest that measurement of hand tapping may indeed enable this. The cross-sectional study of the newer device, whilst not a replacement for longitudinal trials, provides further observations that suggest two tapping parameters (total number of taps and variability of inter-tap interval) may be able to fulfil this role. Firstly, the HD and control values of these parameters are significantly different; secondly, both measures correlate with motor UHDRS assessment of disease severity; and thirdly, they are reproducible. Furthermore, and of vital importance for real life clinical practice, they are quick and extremely inexpensive to measure, entirely objective and require no training (unlike the motor UHDRS assessment). Finally, assessment of tapping is easy at virtually all stages of disease since the instruction and action required are so straightforward.

The measurement of hand tapping is proposed as an objective adjunct to the clinical assessment of patients, not as a replacement for existing assessments. One of its strengths, however, is that no subjective rating is necessary, in contrast to calculating the UHDRS. Furthermore, assessment of voluntary movement has been shown to correlate with the functional disability experienced by patients [2, 7, 20, 21]. It is acknowledged, however, that a weakness of the tapping assessment is its reliance on upper limb function in a disease that can affect the limbs differentially.

Of course the current study needs to be expanded to determine how useful the test is in very early and late disease. Further longitudinal data are required to try to detect subgroups of patients that progress rapidly or slowly. In such longitudinal trials, especially those testing the efficacy of new therapies, the effect of symptomatic medication on tapping score must be taken into account. It may be helpful to alter either the testing equipment or paradigm, for example it might be that extending the duration of testing from 30 seconds to one minute may enable clear detection of fatigue in HD subjects. Eventually it is envisaged that the main use of this device will be as part of the routine objective assessment of clinical phenotype, both in the clinic and during clinical trials.

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