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# Measurement of bradykinesia and chorea in Huntington's Disease using ambulatory monitoring

Katya Kotschet [a], Sarah Osborn [a,b], Malcolm Horne [a,b,*]

[a] Department of Clinical Neurosciences, St Vincent's Hospital, Fitzroy, Vic, Australia
[b] 3065Parkinsons Laboratory, Florey Institute of Neurosciences and Mental Health, Parkville, Vic 3010, Australia

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ABSTRACT

*Objectives:* The feasibility of measuring bradykinesia and chorea in Huntington's Disease using a wearable sensor system (Parkinson's Kinetigraph: PKG) developed for measuring bradykinesia and dyskinesia in Parkinson's Disease was assessed.

*Methods:* Unified Huntington's Disease Rating Scales (UHDRS) and a PKG were obtained for 25 people with Huntington's Disease. Bradykinesia and Chorea Score were derived from relevant sub-scores of the UHDRS and compared with the PKG's bradykinesia and dyskinesia scores. The PKG's daytime sleepiness score was also used.

*Results:* There was good correlation between Chorea Scores and the PKG's dyskinesia score (Pearson's $\rho = 0.66$). Correlation between the Bradykinesia Scores and the PKG's bradykinesia score was also good (Pearson's $\rho = 0.51$) in cases whose PKG scores were in the normal or bradykinetic range. The PKG's bradykinesia score of 23, which is in the higher range of control subjects, separated participants into those with Independence Score $\geq 80$ or $< 80$ and a Functional Assessment (FAS) score $\geq 18$ or $< 18$. The PKG's daytime sleep score was high in 44 % of participants, whose average time asleep was 21 % compared to 1.6 % in participants with a normal sleep index. Participants with high sleep scores were significantly more likely to have low Independence and TFC scores.

*Conclusions:* Measures of bradykinesia and dyskinesia from clinical scales have acceptable correlations with those from the PKG. Continuous monitoring provides information about daytime sleep, which was associated with lower functional status. Further studies and larger sample sizes are required to confirm these findings and the utility of this measure in Huntington's Disease.

## 1. Introduction

Huntington's disease (HD) is an inherited and progressive neurodegeneration that results in progressive motor and cognitive impairment [1] and is caused by an increased number of CAG trinucleotide repeats in the huntingtin gene. The number of CAG repeats predicts the age and probability of HD onset [2]. As reviewed by Ferguson et. al. [2] there is an active interest in developing disease modifying therapies that lower mutated huntingtin gene product. Consequently, there are several clinical trials underway, and several candidates are in the pipeline.

Successful clinical trials depend greatly on suitable end points. The Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMS) is currently an important end point in trials. It is a modified version of the clinical assessment of the motor features of HD and rates the severity of chorea, bradykinesia, dystonia and postural stability. It is affected by inter- and intra-rater variability, subjective bias, and categorical design. It also is carried out in the clinic as a single point measurement rather than in the usual domestic environment of the person with HD. A more consistent and accurate measurement will reduce variation and has the potential to reduce the duration, sample size and cost of clinical trials.

The purpose of this study was to use the Parkinson's KinetiGraph (PKG, Global Kinetics Corporation™, Australia), a system that is currently in use for measuring bradykinesia and dyskinesia in Parkinson's Disease. Chorea is the main feature of the dyskinesia of PD[3] and so the PKG's dyskinesia measurement is likely to be a useful measure of chorea in HD, and bradykinesia of HD and PD are similar [4]. The PKG system consist of a wrist worn data logger containing sensor, sufficient memory to record triaxial accelerometry data continuously for 6–10 days and cloud-based algorithms that provide the bradykinesia and

* Corresponding author at: Department of Clinical Neurosciences, St Vincent's Hospital, Fitzroy, Vic, Australia (M. Home).
*E-mail address:* malcolm.horne@florey.edu.au (M. Horne).

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dyskinesia scores (described in Methods).

## 2. Method

Twenty-five people with HD who attended the State-wide Progressive Neurological Disease (PND) Service at Calvary Health Care Bethlehem Hospital (Melbourne), gave written consent to participate. The Calvary Health Care Bethlehem (CHCB) Research Ethics & Ethics Committee (REEC) approved this study. The study was carried out in accordance with the guidelines issued by the *National Health and Medical Research Council of Australia* for Ethical Conduct in Human Research (and in accordance with the ethical standards laid down in the 196 4 Declaration of Helsinki and its later amendments. The demographics and scores on ratings scales are shown in Table 1. There was no change in medication, including those that would later chorea, immediately prior to or during this study.

### 2.1. Unified Huntington's Disease Rating scale (UHDRS)

All subjects were assessed by one clinician (KK) using the UHDRS. The Combined Limb Bradykinesia scores from the UHDRS were highly correlated with the Finger Tapping score (Pearson's $\rho = 0.91$), the Pronation/Supination score for tone (Pearson's $\rho = 0.93$), Gait score (Pearson's $\rho = 0.73$), and the Body Bradykinesia score (Pearson's $\rho = 0.75$). This indicates that each of these scores carried very similar information, so the sum of the limb and body bradykinesia scores were used as the "Clinical Bradykinesia Score". Similarly, there was a high correlation between the Chorea score of the Right upper limb and the Left upper limb (Pearson's $\rho = 1.0$), the Right lower limb (Pearson's $\rho = 0.73$), the Left lower limb (Pearson's $\rho = 0.71$) and Trunk (Pearson's $\rho = 0.69$). These scores were summed and referred to as the "Clinical Chorea Score".

UHDRS Functional Abilities assesses functional level and the 3 subscores - Functional Assessment (FAS- functional checklist, yes/no score), Independence Scale (IS) and Total Functional Capacity (TFC) were used. The UHDRS Functional Abilities is the sum of FAS and IS [5].

### 2.2. The PKG system

As its name indicates, the Parkinson's KinetiGraph system was developed for measurement of motor features of Parkinson's Disease. It consists of a wrist-worn data logger, a series of algorithms that produce data points for bradykinesia and dyskinesia [6] every 2 min of recording and a report (or PKG), which plots these two-minute scores against the time of day [6–10]. Participants that did not wear the PKG for at least 4 days were excluded from the study.

The PKG's Bradykinesia Score (BKS) refers to the level of bradykinesia, estimated by applying algorithms to each 2 min of accelerometry data [6]. Data is typically collected for 6 days and the median of BKS (mBKS) between 09:00–18:00 was used in this study as a representation of the overall level of bradykinesia for that subject. The mBKS is estimated from data obtained while the logger was worn: a capacitive sensor detects whether the logger is on the wrist. BKS $\geq 80$ are consistent with the subject being asleep and are removed when estimating mBKS. mBKS $> 40$ but $< 80$ are associated with inactivity and an adjusted BKS (aBKS) in which mBKS $> 40$ are removed was also used.

The PKG's Dyskinesia Score (DKS) refers to the level of dyskinesia, estimated by applying algorithms to each 2 min of accelerometry data [6] and the mDKS is the median of DKS between 09:00–18:00, while the logger was worn and over the 6 days of recording, and was used in this study as a representation of severity of chorea. The dyskinesia algorithm recognizes dyskinesia when movements have a mean spectral power in the 0.2–4 Hz range that is above average and with shorter or few periods without movement[6]. Although there is little information about the mean spectral power of Huntington's chorea, it is likely to have similar spectral characteristics to PD and hence, the PKG's DKS was used to measure chorea.

The PKG's scores are constructed using data from people with PD and from non-PD subjects. Bradykinesia is associated with BKS that are above a normal (i.e. control) range whereas dyskinesia, and presumably chorea, is associated with BKS below this normal range. In effect, the presence of chorea (or dyskinesia) can lower the BKS, thus obscuring concurrent bradykinesia. This is particularly the case with dyskinesia consisting of rhythmic wrist movements of frequencies lower than ~ 2.5 Hz, which can overstate the dyskinesia relative to clinical scales and are more likely to lower the PKG's bradykinesia score. The point being made is that in some cases but not necessarily all, chorea could artifactually lower the PKG's bradykinesia score. As bradykinesia is uncommon in the presence of dyskinesia, this is not a significant problem in PD, although in HD, chorea can co-exist with bradykinesia. Thus, it is possible in HD that when high dyskinesia scores are identified by the PKG system, there will be uncertainty regarding the true severity of any bradykinesia that has also been identified.

Percent Time Immobile (PTI) is the PKG's marker of daytime sleep [7,8]. BKS $> 80$ indicate 2 min of no movement of the upper limb and have been correlated with daytime EEG recordings [7]. These studies showed an upper range of 6 % in controls $> 60$ years old and this range has been used in this study, although the age of participants in this study is younger.

The PKG does not have a measurement for the posturing related to dystonia because the PKG only uses accelerometers as sensors, rather than gyroscopes. Movements related to dystonia would be difficult to separate from normal movement using only frequency range.

### 2.3. Statistics

Most data were normally distributed, so mean and standard deviation were used to describe distributions except in instances where nonparametric distribution affected interpretation. Populations were compared using a two tailed homoscedastic T-test and the Cohen's D statistic was used to estimate effect size.

**Table 1**
The demographics of participants and their scores on ratings scales.

| | Mean ± S.D. | Range |
|---|---|---|
| Age (years) | 59.8 ± 12.1 | 29–81 |
| Age (years) at Symptom onset | 42.3 ± 2.5 | 27–76 |
| Duration of disease (years) | 6.4 ± 4.6 | 1–20 |
| CAG length | 42.3 ± 2.6 | 39–47 |
| UHDRS-TMS | 36.3 ± 15.9 | 10–71 |
| FAS | 17.2 ± 6.7 | 1–25 |
| IS | 75.6 ± 13.3 | 50–100 |
| TFC | 6.8 ± 4.2 | 0–13 |
| Functional Abilities | 92.8 ± 19.5 | 51–125 |

Abbreviations are described in Methods.

## 3. Results

### 3.1. Relationship between Clinical bradykinesia Score, Clinical chorea score and the PKG measures

The Clinical Bradykinesia Scores were plotted against the PKGs score for bradykinesia (mBKS) adjusted to remove inactivity (aBKS) and the Clinical Chorea Scores were plotted against the PKG's score for dyskinesia (mDKS) (Fig. 1). The cases represented by red circles in Fig. 1A have a high mDKS (≥7, presumably due to chorea). As discussed in the Methods, a high DKS may obscure the extent of coincident bradykinesia. When aBKS $> 15$, there is a broad relationship between aBKS and Clinical Bradykinesia Scores and if the circled cases in Fig. 1A are excluded, the Pearson's is $\rho = 0.51$. In the absence of a high mDKS, the aBKS would all be moved to the right (i.e. a higher aBKS) depending on the coincident bradykinesia.

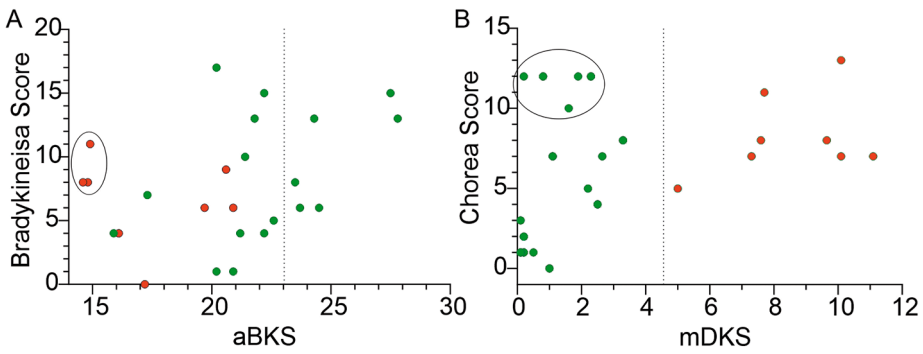


**Fig. 1.** Comparison of clinical scales for bradykinesia and chorea and PKG scores for bradykinesia and chorea Fig. 1 A is a plot of the Clinical Bradykinesia Scores (Y axis, Fig. 1A) against the aBKS (X axis). The red circles in Fig. 1A are cases mDKS is high (≥7, presumably due to chorea) and affecting the assessment of bradykinesia by the aBKS in these cases. Fig. 1B is a plot of the Clinical Chorea Score (Y axis) against the mDKS score (X axis). See text for discussion regarding cases in the circle. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

When the Clinical Chorea Scores were plotted against the mDKS, there was a broad relationship with mDKS. Note that one case with a very high mDKS (>20) and low Clinical Chorea Score was excluded because the PKG's spectrogram suggested that increased activity was likely due to non-physiological factors such as operating equipment. There were 5 cases with high Chorea Score but low mDKS (in circle in Fig. 1B). It is hypothesized that these are cases whose levels of chorea are much higher in the clinic than at home (hence a low mDKS which is a measure of usual domestic levels). The correlation between Chorea Score and mDKS was high (Pearson's $\rho = 0.66$) when cases in the circle are excluded.

### 3.2. Relation between Functional scales for HD and the PKG scores

An mBKS of > 23.5 or ≤ 23.5 best separated subjects according to whether their Independence Score was ≥ 80 or < 80 (Fig. 2), noting that an IS ≤ 80 indicates difficulty in performing household chores, managing finances and loss of employment at pre-disease level and is indicative of dementia [11,12]. This level of mBKS also sorted subjects according to whether their FAS was ≥ 18 or < 18. Using an mBKS ≤ 23.5 as the sorting criteria, there was a statistically significant difference between the functional and motor scores with large effect sizes (Cohen's D) (Table 2). There was a statistical difference ($p < 0.05$) for FAS and TFC, with large effect size (Cohen's D).

The mDKS were sorted on the same criteria (FAS ≥ 18 or < 18 and independence scale ≥ 80 or < 80, Fig. 2b). The mDKS was significantly higher when FAS scores were>18, indicating that chorea measured by mDKS was associated with a higher FAS score whereas the Clinical Chorea Score was not statistically significant (Table 2). A similar but non-significant relationship was seen with the mDKS and the Independence Score. Most people (~75 %) with FAS < 18 or IS < 80 did not have an elevated mDKS, implying that significant chorea was not present when these scores were low.

**Table 2**
Functional and motor scores sorted according to whether the mBKS was>23.5 or less than or equal to 23.5.

| | mBKS ≤ 23.5 | mBKS > 23.5 | | |
|---|---|---|---|---|
| **HD Variable** | **Mean ± S. D.** | **Mean ± S. D.** | **Cohen's D** | **P Value** |
| FAS | 13.5 ± 7.3 | 20.1 ± 3.9 | 1.01 | 0.01 |
| IS | 69.1 ± 13.8 | 80.7 ± 9.6 | 0.90 | 0.03 |
| TFC | 5.0 ± 3.9 | 8.2 ± 3.7 | 0.79 | 0.05 |
| Functional Abilities | 82.6 ± 20.7 | 100.9 ± 12.9 | 0.96 | 0.02 |
| Luria | 2.4 ± 1.3 | 1.6 ± 1.1 | −0.63 | 0.13 |
| UHDRS-TMS | 43.8 ± 14.4 | 30.4 ± 13.9 | −0.86 | 0.03 |
| Clinical Bradykinesia Score | 10.2 ± 4.9 | 5.9 ± 3.1 | −0.95 | 0.02 |
| Clinical Chorea Score | 5.8 ± 4.7 | 7.4 ± 3.1 | 0.39 | 0.35 |

Abbreviations are described in Methods.

### 3.3. Indirect measures of daytime sleep (Percent time Immobile: PTI)

Percent Time Immobile (PTI) is a marker of daytime sleep [7,8] with an upper range of 6 % in controls > 60 years old. The median in this population was 4 %, but the range was 0.1 % to 42 % (Fig. 2C). In subjects with a PTI ≤ 6 %, the average time asleep was only 1.6 % of the day (S.D = 1.5) whereas those with PTI > 6 % (44 %), the average time asleep was 21.6 % of the day (S.D = 13.1). The people with high PTI had significantly lower IS (70 ± 13.5c.f 80 ± 10.7p = 0.03, *T*-test) and TFC (83 ± 20.2c.f. 99.6 ± 15; p = 0.02, *t*-test). Only 9 % of people with a High PTI had an IS > 80 (Fig. 2C).

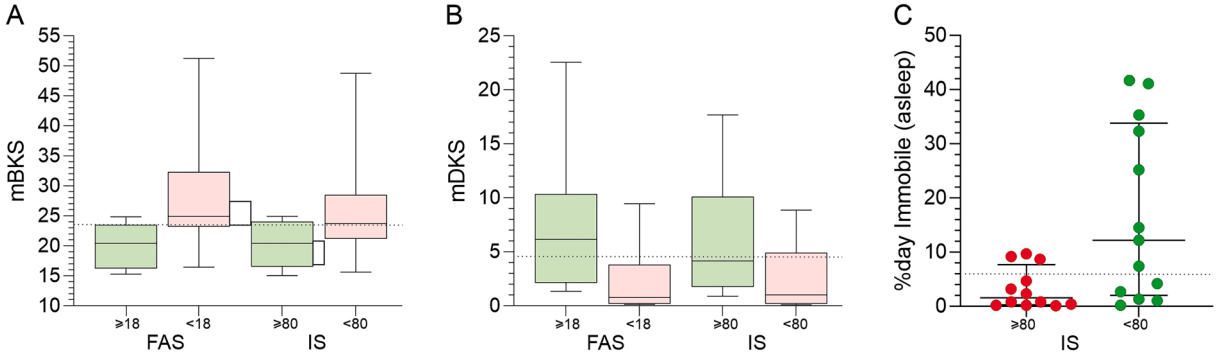


**Fig. 2.** Fig. 2A and 2B show mBKS and mDKS scores for each individual sorted according to whether the FAS score was greater or equal to 18 or the IS score was greater or lower than 80. The dotted line shows mBKS = 23.5 and mDKS = 4.5 respectively. Fig. 2 A and B are box plots showing the median, 25th and 75th percentile with the whisker showing 10th and 90th percentile. Fig. 2C shows the PTI (percent o day immobile or asleep) sorted by participants having an IS > 80 or ≤ 80. The dotted line showing the upper range of PTI in controls.

## 4. Discussion

The purpose of this study was to assess the utility of the PKG in measuring the motor features of HD. There was a broad correlation between the PKG's bradykinesia score (aBKS) and the sum of the limb and body bradykinesia scores provided by the UHDRS-TMS. Activity such as chorea or dyskinesia can lower the aBKS score and thus obscure the severity of concurrent bradykinesia. While this is not a problem in PD, chorea and bradykinesia can co-exist in HD and may explain why 3 subjects in this study have high UHDRS limb and body bradykinesia scores yet low aBKS. While it is also possible that the bradykinesia was underestimated by the aBKS in all 8 of the subjects with high mDKS (red dots in Fig. 1A), it is unlikely that this was significant because most other points lay on a line with good correlation with the clinical bradykinesia score. As suggested in the Methods, there may be chorea with specific frequency characteristics particularly affecting the wrist, which cause the mismatch in bradykinesia scores in the 3 cases in the circle in Fig. 1A: unfortunately, we do not have data to interrogate this question. There was also a broad correlation between the PKG's dyskinesia score (mDKS) and the UHDRS limb chorea score, although there were cases whose mDKS was lower than would be expected from the chorea score. It is well accepted amongst clinicians that anxiety and stress, including attendance at a clinic, increases the amount of chorea. This suggests that continuous unobtrusive measurement of subjects at home may give a more accurate representation of the level of chorea.

As the PKG scores were designed to measure features of PD [6], it is relevant to consider their suitability for measuring motor features of HD. The bradykinesia of HD is very similar to that of PD with distal bradykinesia, rigidity and postural instability [4], and as with PD, the severity of bradykinesia in HD correlates well with putaminal D2 binding[13]. Thus, the PKG's BKS should accurately detect bradykinesia of the limbs. As the axial scores and lower limb scores correlated highly with the upper limb scores in the participants in this study, the BKS would be expected to also provide a measure of bradykinesia in HD. Dyskinesia in PD is an umbrella term for choreic and dystonic movements induced by levodopa with choreic movements being the most common [3], so the mDKS is effectively measuring choreic movements[6]. There is very little published information about the frequency range of chorea in HD, but visual inspection suggest it is similar or marginally slower than that of PD and that it falls within the frequency range 0.2–4 Hz of the PKG system and is captured by its dyskinesia algorithm. The PKG system is not able to measure dystonia although it is unclear whether this is an important independent measure of outcomes in HD. Some recent approaches have used machine learning to produce scores that accommodate chorea, bradykinesia and dystonia, without explicitly addressing which motor features are contributing to the severity of the score[14,15]. The Q-Motor measures [16] use tests that measure all aspects of motor disabilities in HD to produce a composite score. It measures performance at the clinic at a specific point in time, whereas a wearable sensor provides measures of a longer periods outside of clinical scrutiny.

Visual inspection of the data indicated that an mBKS $> 23.5$ sorted subjects according to whether there IS $\geq 80$ or the FAS was $\geq 18$ or $< 18$. This is relevant because scores below these scale levels indicate loss of independence and dementia [11,12] and current UHDRS motor scores do not relate motor impairment to daily life. In keeping with other studies, subjects with higher Clinical Bradykinesia Scores had worse function than those with high Clinical Chorea Scores [17 12]. While it is not being proposed that these motor scores would replace the direct functional measurement, they are being discussed because they provide some validation of the instrumented measure [14]. The mBKS that provides this cut-off is lower than the target for treating PD [18] set for older subjects, though they do lie at the 75th percentile for controls of a similar age group to those in this study (unpublished data).

Continuous monitoring of movement also provides the opportunity to measure surrogates of daytime sleep (PTI). This showed that those who had increased daytime sleep were also far more likely to have an IS value in the dementia range (<80). Gait can now be measured with the PKG [19], and future studies comparing step count, PTI and measures of apathy and cognition may prove to be of interest. A previous study using a wearable sensor also showed that inactivity was more than in control population [20].

There are several limitations to this study. The number of participants is small, and the reproducibility of these findings should be addressed in a larger study. The effect of chorea on the PKG's bradykinesia scores could be a significant drawback and further studies are required to assess what aspects of chorea specifically causes this problem, the proportion of choreatic subsects affected and whether the PKG's algorithm could be modified to overcome this. The PKG is unable to assess dystonia in HD. Loggers with gyroscopes would be required and even then, it may not be possible without multiple sensors. This highlights a further difficulty facing long-term monitoring using sensor: the greater the number of sensors the lower the patient's compliance in wearing the loggers. While there was good correlation between motor disturbance in a single limb and the total score in the cohort used in this study, further studies are required to confirm the extent that information is traded off for increased compliance using a single data logger. The main reason for using sensor worn at home over several days is to gain information that is not apparent in the clinic, such as daytime sleep and inactivity. Further studies are required to resolve whether some patients do indeed suffer from "white coat" chorea or whether there is underestimation of chorea by the PKG in some subjects.

## 5. Conclusions

Objective measurement using the PKG's measure of bradykinesia and chorea provide correlations with clinical scores, especially if it proves to be the case that an objective measure of chorea is more reflective of the usual level of chorea at home than clinical assessment. A major issue when interpreting the PKG's measure of bradykinesia is that it appears to understate the level of bradykinesia when the mDKS is high. An mBKS of 23.5 and a high PTI sort subjects into those with high and low levels of independence. This study provides support for a larger study of objective measurement in HD to confirm whether the PKG scores could be used a clinical trials endpoint.

**Author contributions**

KK and SO recruited and collected data related to clinical scales. SO, KK and MH were involved in analyses and MH wrote the manuscript. All authors reviewed the paper.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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