

The Clinical validation of objective Measurement of Movement in Parkinson's Disease

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A B S T R A C T

Introduction

Home based objective measures of bradykinesia and dyskinesia will be important in managing Parkinsons Disease (PD). The Aim of this paper was to further validate the Parkinsons Kinetigraph system as a tool for measuring bradykinesia and dyskinesia by examining its capacity capture the effect of therapeutic interventions, detect bradykinesia and asymmetry in a newly diagnosed patients, and correlates with relevant clinical scales and its repeat reliability.

Methods

Data was obtained from patients who had used the Parkinsons Kinetigraph as part of routine clinical care or in other unrelated studies and for whom clinical scales (where relevant) were also available. The results are presented as a separate studies.

Results

A change in dyskinesia following insertion of Deep Brain Stimulators was observed and was commensurate to the changes obtained by clinical scales. A consistent change in bradykinesia and dyskinesia following levodopa was measured in patients with fluctuating PD. Bradykinesia was measured in newly diagnosed and differed from controls with a Sensitivity of 100% and Selectivity of 83% (Area under Receiver operator curve of 0.96). Asymmetry was greater than controls in 56%, which broadly correlated with differences found with clinical scales. We found that five days of recording produced a consistent bradykinesia score with a 6% standard error.

Conclusion

In this paper we provide data from a series of studies that show that the PKG system provide further validation that it could be used in routine care of Parkinsons Disease (PD).

Keywords: Parkinson's Disease, objective measures, dyskinesia, bradykinesia, ambulatory monitoring.

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INTRODUCTION

Recently we described the Parkinson's Kinetigraph (PKG), which is an accelerometry based system for long term automated assessment of dyskinesia and bradykinesia(1) in patients with Parkinson's disease (PD), whose scores of bradykinesia and dyskinesia correlated with the Unified Parkinson's Rating Scale part III (UPDRSIII) and the modified Abnormal Involuntary Movement Score (AIMS) respectively. The problem in validating a new system for measuring bradykinesia and dyskinesia, such as this, is that the experienced Movement Disorder clinician is the gold standard and rating scales were developed

to quantify and standardise the clinician's assessment. While they have high internal consistency and inter-rater reliability(2) they only measure a clinical state at a point in time, and fail to capture the variation in the clinical state that occurs across the course of the day, and from day to day. As motor fluctuations or daily medication off-times are linked to poorer quality of life, diaries were developed to capture these fluctuations(3, 4). Diaries have many well documented shortcomings(5) but in particular, they are a subjective presentation of clinical scores compared to the more objective assessment provided by a clinical assessment. The PKG is designed to provide an objective assessment that correlates with rating scales and provides

this assessment over the course of the day and in relation to the timing of medications.

While the PKG has been compared with clinical rating scales(1), this is only a component of a broader validation required of a measuring tool for PD. For example, clinical scales themselves have been validated by their repeat reliability, their capacity to detect the effect of effective therapies, or accepted clinical deficits. The UPDysRS was compared with other measures of dyskinesia in detecting the effect of amantadine in depressing dyskinesia(6) or to detect changes detected by a clinician in a newly diagnosed case. Rather than seeking validation in comparisons with only clinical rating scales, in this study we have examined the PKG's capacity to measure in a number of ways. We examine the repeat reliability of the PKG in recording over several days and in repeated measures of the response to levodopa. Measurement of the response to DBS is described and a comparison between the PKG and the clinician's detection of newly diagnosed subjects is described. Finally, comparison with clinical rating scales from a larger cohort than in the initial study(1) are presented. A key tool in the assessment of bradykinesia and dyskinesia in clinical trials is the diary. We have not included comparisons with the diary here because they are the subject of a submitted manuscript which showed moderate-to-high overall concordance with patient's diary data(7).

METHODS

All assessments included the use of the PKG and clinical rating scales were performed as part of routine care or as part of disparate research studies which received approval from the St Vincent's Hospital Human Research Ethics Committee. This committee provided approval (numbers HREC-A 152/09; HREC/12/SVHM/11; QA 072/14) to review the medical records of patients whose data has been used in this paper and waived the need for written informed consent from the participants and records and information was made anonymous and de-identified prior to analyses. All subjects had either idiopathic Parkinson's Disease (PD) or were age matched controls, aged greater than 45 years and without PD or other neurodegenerative disorder.

THE PKG

The PKG (Global Kinetics Corporation) consists of a wrist worn data logger that contains an accelerometer and memory sufficient for 10 days of continuous recording. The PKG was worn for at least 6 days on the wrist of the most affected side, or on both wrists in the case of newly diagnosed patients and controls. When recording was completed, data was downloaded and analysed by proprietary algorithms that calculate a bradykinesia score (BKS) and a dyskinesia score (DKS)(1) every two minutes. Thus in one day, between the hours of 0900-1800, there are 270 DKS and BKS and 1620 in 6 days. The median of these scores is referred to as the median BKS and DKS for that individual. The BKS and DKS do not have normal distributions (Supplementary Figure) and can be described

by their means and interquartile ranges (IQR). Note that BKS and DKS can be used to describe movements of both non PD (controls) and PD subjects, and difference between patients and controls can be described by differences in the means and IQR of their DKS and BKS (Supplementary Figure 1). The median BKS and DKS describe the central tendency of each distribution and Griffith et al(1) showed that the median BKS and DKS correlates with the UPDRS III and the AIMS respectively (elaborated further in results). Two other related variables that describe the shift in the BKS and DKS to higher scores with increasing severity of bradykinesia or dyskinesia are the number of BKS values that lie above the 50th percentile of controls (BKS^{>50}) and the number of DKS values that lie above the 75th percentile of controls(DKS^{>75}). By definition this is 50% and 25% respectively, for control subjects. Because each BKS is 2 mins in duration, the difference between the patient's BKS^{>50} and that of controls (i.e. 50%) represents the reduction in time spent in the "normal" state: in other words, it is an indication of "OFF" time. Similarly the extent to which the patient's DKS^{>75} is greater than that of controls (i.e. 25%) is indicative of the increase in time spent in the dyskinetic state.

The PKG is also programmed to provide a reminder, in the form of a brief vibration, at the time of prescribed doses of levodopa. Patients could acknowledge on the PKG when the dose was consumed.

CONTROL SUBJECTS

The median of BKS and DKS of normal subjects was established by recruiting 50 subjects without PD or other neurodegeneration, orthopaedic or mobility impairment and aged 45-85 (12 in each decile). They were asked to wear the PKG for at least six days and to refrain from operating a device or machine (e.g. a walking aid, or machinery) that would constrain or move the hand involuntarily (as per instructions to patients when using the PKG). Fifteen subjects were excluded: 7 for wearing the PKG for 3 days or less and 8 as outliers (> 2 standard deviations: BKS=1, DKS=7). In at least two subjects it is likely that the use of power tools such as industrial cleaners (that moved the limbs repetitively) caused these high scores. Thus further analyses were performed on 35 subjects (See Table 1).

RATING SCALES

The UPDRS III and AIMS were obtained in the "ON" state immediately prior to wearing the PKG logger for 6-10 days. Unless otherwise stated, AIMS was obtained while the subject was actively performing a task. The UPDRS III(8) includes ratings of bradykinesia, rigidity and tremor(9, 10), with tremor comprising ~26% of the score. As tremor does not always accompany bradykinesia and its severity may vary independently of bradykinesia, tremor scores were removed from the UPDRS III (referred to as UPDRS III-T). A UPDRS III-T>45 indicates very severe bradykinesia. A modified AIMS, recorded in the active state and consisting of a five-point severity scale from 0 = none to 4 = severe for both arms, both legs, the trunk and head was used (referred to here as AIMS).

Table 1. PKG parameters in normal subjects

BKS 25%	Median BKS	BKS 75th	DKS 25%	Median DKS	DKS 75th
11.6	17.2	25.5	0.6	3.1	15.1

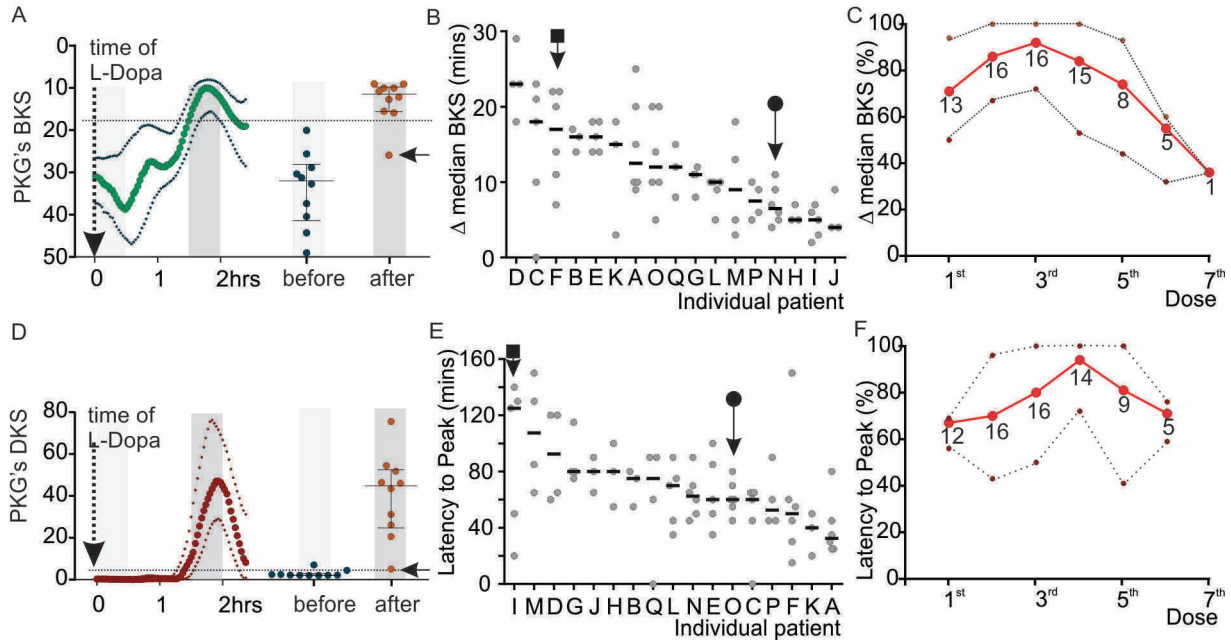


Figure 1.

A and D: are examples of how the response to a dose was evaluated. They show the PKG's BKS (A) and DKS (B) in the 150 minutes following a dose. The heavy lines represent the median value and the lighter lines the 25th and 75th percentile of 10 days of recording. The horizontal dotted lines represent the median of normal subjects. The median value of the 15 BKS and DKS occurring in 1-30 minutes after dose (blue dots) and 90-120 minutes after dose (red dots) was estimated and shown in adjacent plots. Note that there was a "dose failure" shown by the arrows. There was a significant difference between the two times of measurement for both dyskinesia and bradykinesia (Mann Whitney $p < 0.0001$).

B and E show the response of 16 subjects who took up to 7 doses in the day. Nine of the 16 took 5 or more doses a day and 3 subjects were stayed in bed after the first dose. B shows the amplitude of the BKS of each dose (as a difference from the average response at the time of taking the meds) and sorted according to subject (X axis). E shows the latency (in minutes) of the BKS of each dose, sorted according to subject (X axis). Arrows with circles show individuals with reproducible responses whereas those with squares are variable.

C and F show the amplitude (C) and latency (F) of each dose normalised to the largest response of each patient. This data suggest that for most patients the largest response and the longest latency occur with the third dose of the day. The heavy red line is the median for all patients and the dotted lines the 25th and 75th percentiles for each dose.

PRESENTATION OF RESULTS

The results are presented as a series of "mini-studies". While the methods that are general to all studies are presented above, those that are unique to each study are presented within the results to aid readability.

RESULTS

The variation of the PKG Measures of Bradykinesia and Dyskinesia in non PD subjects.

As the bradykinesia and dyskinesia of people with Parkinson's disease is described by the extent to which the means and interquartile ranges (IQR) of their DKS and BKS differ from control subjects (Supplementary Figure),

the characteristics of these values in normal subjects is relevant. The median DKS and BKS values of normal subjects were plotted against age and there was a non-significant trend for the BKS to rise with age and for the DKS to fall with age.

We also examined how many days of recording were required for a normal subjects median score to regress toward a median values (noting that the distributions are non-parametric) – this is in effect a measure of repeat reliability. In the case of the BKS, the standard error (SE) for one day of recording was 2.62 BKS (median 17.2) and the SE asymptoted at 1.1 after 5 days of recording (i.e. 6% of the median BKS). As the variance of the BKS is not altered by an increasing mean (i.e. increasing bradykinesia), 5 days of recording will provide a reliable

TABLE 2: Statistics for DBS

	UPDRS III		AIMS		Median BKS		Median DKS	
	before	after	before	after	before	after	before	after
No	15	14	15	14	15	15	15	15
Median	25	11.5	4	0	18.2	20.2	13.96	2.3
IQR	20	14	8	0.25	8.1	5.9	21.84	7.9
P value*	0.08		0.01		0.17		0.01	

* Mann Whitney

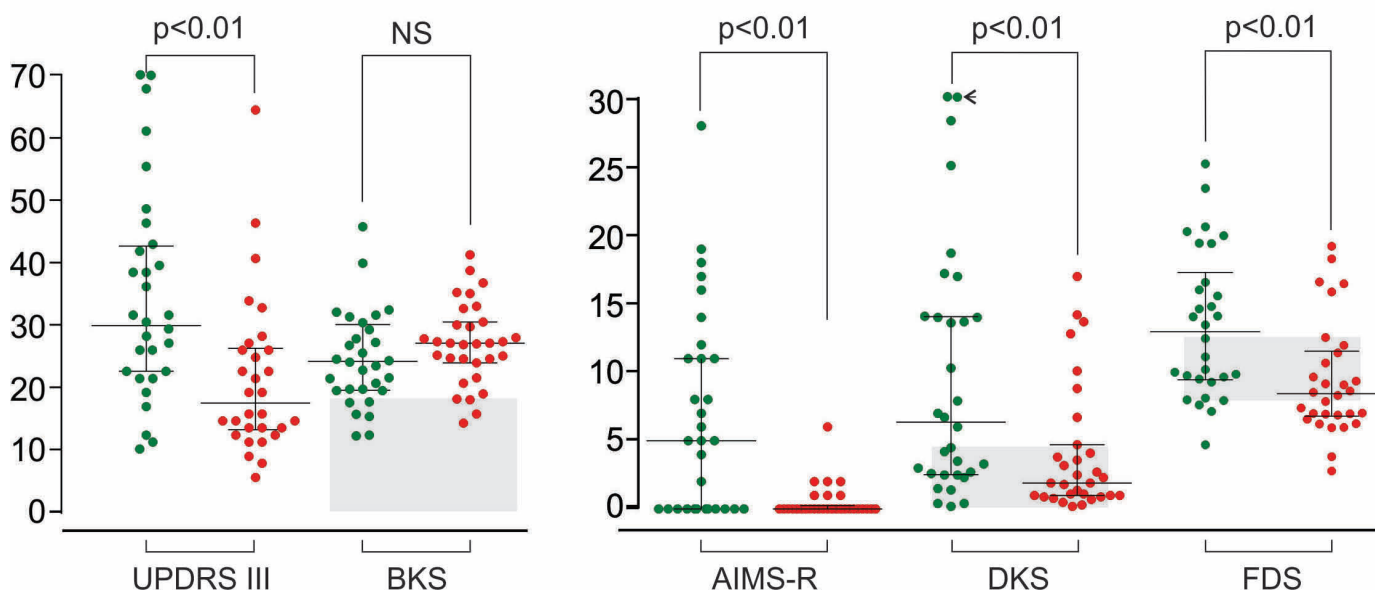


Figure 2.

Graphs showing the median and interquartile range of changes in rating scores and PKG measures before and six months after DBS in 30 PD patients. In each plot, the Y axis is the relevant value of the scale or PKG measure. Before DBS is shown as green circles and After DBS as red circles. NS= non-significant and the p values are derived using Mann Whitney.

estimate of the mean for all subjects. The SE after 5 days of recording corresponds to ~1.5 UPDRS III points(1) (see also Figure 4).

In the case of the DKS, the SE for recording from a single control subject was 0.9 DKS (median 3.09). This was not improved by increasing the number of days of recording and represents a 10% standard error. Unlike the BKS, the variance of the DKS remains constant with the logarithm of the mean, meaning that there is greater uncertainty around the mean when the DKS is high. Thus when the median DKS is close to that of normal subjects (i.e.<5 and corresponding to an Aims of <4), the SE represent ~1/2 an AIMS unit but when the median DKS is high (i.e. 30 DKS and corresponding to an AIMS of ~21), the SE represent ~4 AIMS units. Thus there is a 10% error in the \log_{10} (Median DKS) (see discussion below).

This is intuitively consistent with clinical observations that as dyskinesia increases, there is much greater intrinsic variation in the patient's state. Note that the SE in this setting captures both the intrinsic variability in the patient as well as any error intrinsic to the measuring system.

The response to levodopa.

The term “predictable fluctuations” in bradykinesia and dyskinesia indicates a predictable but not necessarily identical response to dose of levodopa. Typically, bradykinesia might improve 30 mins after a dose, with dyskinesia peaking around 60 minutes later (90 mins after the dose)(11). An effective measure of bradykinesia and dyskinesia should quantify such fluctuations. Sixteen subjects whose motor fluctuations were predictable and associated with loss of early morning sleep benefit were studied. As described in the methods, patients acknowledged consuming a dose of levodopa following a reminder at scheduled times. In the 30 minutes after the acknowledgement there are 15 BKS and DKS (calculated every 2 minute) and for each dose taken by each patient, the median value of these BKS and DKS was calculated as a measure of the patient's “OFF” state (Figure 1). Similarly the 15 BKS and DKS occurring between 90-120 minutes after the dose were calculated to provide the “ON” scores (Figure 1A and D). The median size of the BKS and DKS response was estimated for each dose. The average time to

reach the peak BKS and DKS response was also estimated (Figure 1A and D).

The response of each dose of levodopa of the 16 subjects was examined. Subjects took between 3 and 5 doses of levodopa a day, although it was not always possible to measure every dose because the patient was asleep or had removed the device. In some subjects, the amplitude or latency of response was similar for every dose, whereas for others it was quite variable (Figure 1B and E). The amplitude and latency of each dose was normalised to the largest response of each patient for that particular dose. The data from all patients was pooled and suggested that for most patients, the largest response and the longest latency occurred with the third dose of the day. In summary, the PKG measures the effect of a single dose of Levodopa at a particular time of day.

Measurement of Improvement Following Deep Brain Stimulation (DBS).

Scores from the PKG and clinical scales obtained before and after DBS were compared in 15 patients (Figure 2). Patients were selected for DBS by their treating neurologist for treatment of dyskinesia and motor fluctuations. The treating neurologist also provided the AIMS and UPDRSIII scores in the "ON" state. Prior to insertion of DBS, the AIMS were greater than 7 in 7/15 cases and the UPDRS III was greater than 25 in 8/15 cases. There was a statistical improvement in dyskinesia as measured by both clinical scales and PKG (Table 2 and in Figure 2). Most patients did not have dyskinesia after DBS according to both the AIMS (12/15) and the median DKS of the PKG (11/15). There was a non-significant trend for both UPDRS III and median BKS to improve (note that these scores were obtained in the "ON" state and so may not show much change).

Can the PKG be used to detect early PD

The diagnosis of PD requires the detection of bradykinesia. We compared the median BKS in 18 newly diagnosed, untreated participants with PD to the median BKS of the 35 control subjects (Figure 3A). The median BKS was lower in patients than in controls (Table 3) and the Area under the Receiver Operator Curve was 0.96 and the Sensitivity and Specificity for making a diagnosis of PD in patients with a median BKS of 25.7 was 100% and 83% respectively. The Median UPDRS III was 15 (range: 5-43). Sixty percent of patients have asymmetry of signs at diagnosis(12). The difference between median BKS of the left and right arm was calculated in the 18 patients and 13 controls (Figure 3B). According to the PKG, 8/10 patients had more asymmetry than found in controls (i.e. difference >5 BKS, which is ~ 4 UPDRS III units). According to the UPDRS III-T (tremor removed), 8/10 patients had a difference in UPDRS III-T >3.

Clinical rating scales

Cases in which a UPDRS III score was obtained prior to the PKG being worn were examined. Cases whose UPDRS III - T (see methods for definition) were greater than 45 were excluded because the PKG algorithms identified many periods of immobility (i.e sleep(13)) providing too few points for reliable correlations with clinical scales. A UPDRS III-T>45 also indicates severe bradykinesia. Cases with a median BKS <16 were also removed: they are invariably associated with significant dyskinesia, which affects the sensitivity of the bradykinesia algorithms. The UPDRS III-T was plotted against BKS^{>50} (Figure 4A). Seven subjects whose BKS lay far outside the 95% confidence limits from the trend line were removed. There were 85 remaining data points (Figure 4A). A linear correlation was performed on the remaining data and producing an r^2 of 0.55. In the same set of 85 subjects, the UDRS III-T was then plotted against the median BKS (Figure 4B) and a linear correlation produced an r^2 of 0.42. Note that the relation may not be linear with greatest correlation being when the UPDRSIII-T is greater than 10 and less 30. Sixteen newly diagnosed patients, most of whom had asymmetric bradykinesia were not included in this study because previous studies(1) showed that the PKG algorithm over estimates bradykinesia compared with the UPDRS III in subjects with early disease. For comparison, their BKS were added to the plot in Figure 4A. Explanations for this disparity are reviewed in the Discussion.

Cases in which a PKG had been worn and an AIMS score was available were examined. The AIMS were plotted against the DKS^{>75} of controls and 11 points were removed because of their distance from the 95% confidence interval leaving 86 data points (Figure 4C). All points whose AIMS were 0 (n=46) were also removed so as to avoid these points biasing a linear correlation. The DKS^{>75} of those whose AIMS=0 was less than 25 in 89% (by definition, 25% of DKS are above the 75th percentile in controls). A linear correlation was calculated on the remaining 40 subjects and had an $r^2 = 0.49$. Using the data from the same set of subjects, AIMS was plotted against the median DKS (Figure 4D), which produced and a linear correlation produced an r^2 of 0.66.

Discussion

At a conceptual level the definition of many physiological and pathological processes are entwined with the way they are measured. For example, diabetes is defined by the blood glucose level, which is intrinsically linked to pathological processes. Terms such as hypertension or bradykinesia carry references in their name to an increase or decrease in blood pressure or movement (respectively), implying that measuring these variables would quantify the physiological disturbance. In the case of bradykinesia and dyskinesia, there is no existing measure that reflects their pathophysiology and thus no gold standard, other than the neurologist. The PKG algorithms were modelled on clinicians' assessment of bradykinesia and dyskinesia and do correlate with the clinical rating scales(1). In this

Table 3

	Median BKS		% time >50% controls	
	Controls	Patients	Controls	Patients
median	17.2	31.5	53.2	13.5
SD	2.8	6.0	11.4	9.9
P Value (t test)	<0.0001		<0.0001	
Selectivity	93.3%		93.3%	
Sensitivity	100%		100%	

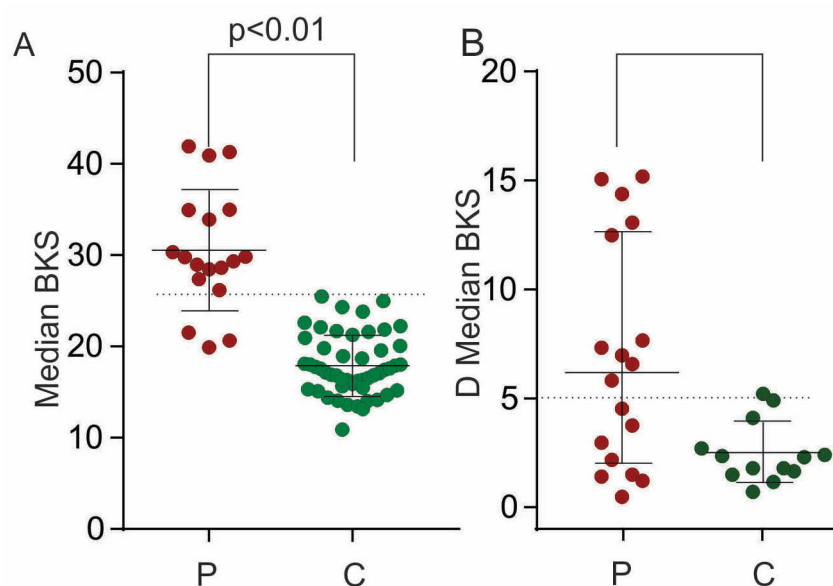


Figure 3.

A: The median BKS values for 35 control subjects (C, green dots) and 15 patients whose PD was newly diagnosed (P, red dots). The red line at a BKS of 25.7, separates controls and patients with a sensitivity of 100% and selectivity of 93.3%.

B: The difference between median BKS on the left and right arm were performed in patients and controls. Not including tremor, the average difference in UPDRS III scores between left and right hand was 1.6 in those with a Δ BKS <5 and was 3.6 in those with a Δ BKS >5.

study we replicate these findings in a larger clinical cohort, but the absence of a readily accessible gold standard argues for the necessity of several different approaches to demonstrating validity.

In this study, we show that PKG algorithms can measure the effect of therapies (DBS and levodopa) and the bradykinesia of early PD as well as the correlation with clinical rating scales. DBS is usually effective in treating dyskinesia as shown here by both AIMS and the DKS. There was a difference in UPDRS III before and after DBS but not BKS and the reason may be because the presence of significant dyskinesia can “pull” the BKS down so that the true level of bradykinesia may be obscured: consequently BKS may actually increase when dyskinesia is reduced. This may have affected some scores. There may also be a difference between observed bradykinesia in the “on” state in the clinic and that measured in routine behaviour at home. As well, a number of the cases had significant tremor that improved after DBS and this would be captured in the UPDRS III but not the PKG’s BKS.

Although the response to levodopa is variable in PD(14), in each individual the change in BKS and DKS following a dose of levodopa was fairly consistent over the course of the day and from day to day. In view of the standard error of the BKS and DKS (shown in this paper), the variability shown here is more likely to be due to variability in absorption rather than in measurement. Similarly, the discrimination, with high sensitivity and specificity, between controls and PD participants that were newly diagnosed by a movement disorder neurologist, is a further example of the PKG’s capacity to discriminate between the same difference in motor state that a clinician can detect. The median UPDRS III of the newly diagnosed was 15 with the lowest score of 5, indicating that relatively subtle changes were detected by the PKG. The PKG worn bilaterally also captured asymmetry in 56% of subjects compared to 59% of subjects having definite asymmetry of signs in the published literature(12).

The relationship reported by Griffith et al(1) of a correlation between the PKG scores and clinical scales

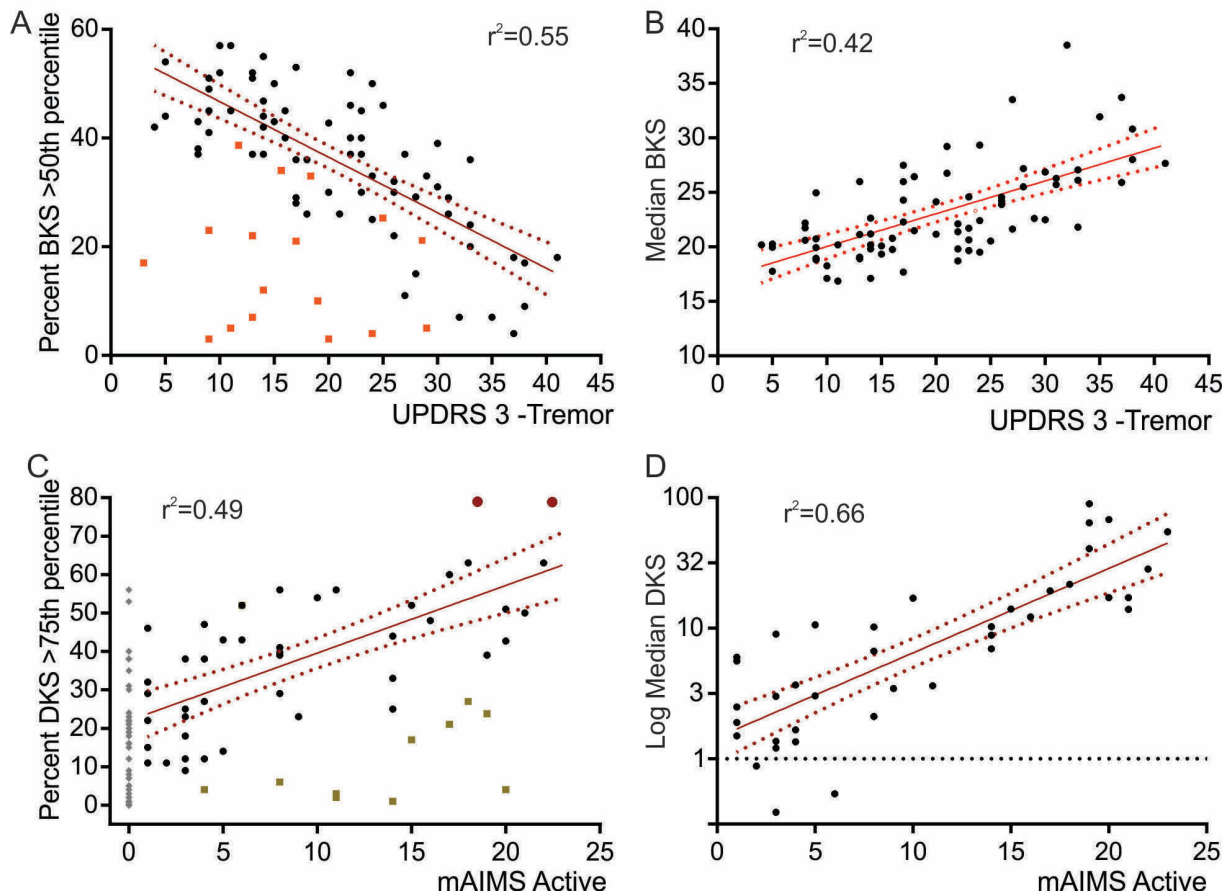


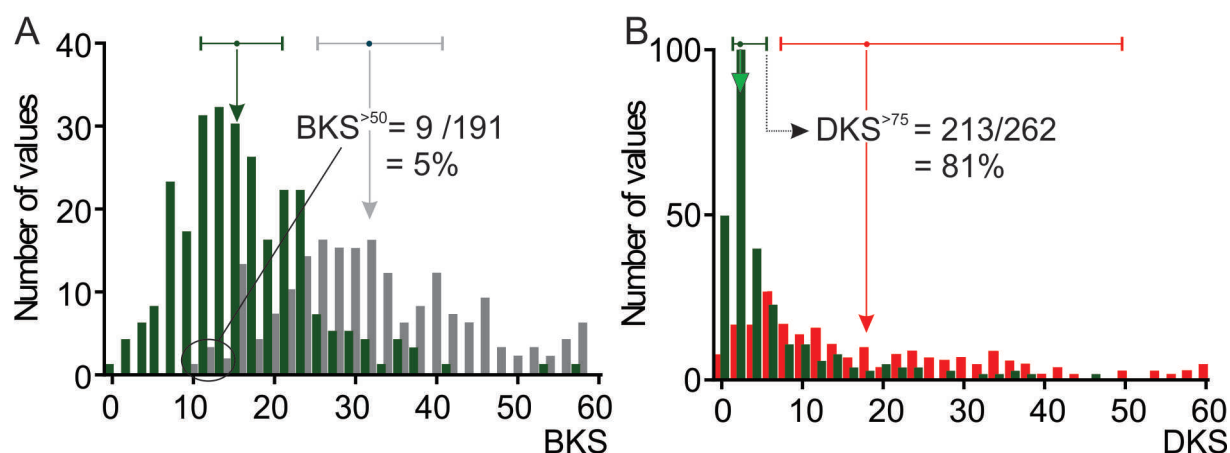
Figure 4.

- A. This is a plot of the percent of BKS >50th percentile of controls plotted against the UPDRS III with tremor scores removed (UPDRS-T) in the “ON” state. Orange squares represent newly diagnosed patients with asymmetry. The correlation has an $r^2=0.55$.
- B. This is a plot of the median BKS plotted against the UPDRS III-T, using the same data set represented by the black dots in B. The correlation has an $r^2=0.42$.
- C. This is a plot of the percent of DKS >75th percentile of controls, plotted against the AIMS Active in the “ON” state. The tan squares represent outliers. The two dots with larger red backgrounds have been clipped to 40 so as to show in the plot. The grey dots show patients whose AIMS score=0 (i.e. did not have dyskinesia) and these have been removed to calculate the linear correlation with an $r^2=0.49$. Note that 89% of the patients whose AIMS=0 also had a DKS >75th percentile of controls of 25% or less (i.e. in the normal range).
- D. This is a plot of the median DKS plotted against the mAIMS Active, using the same data set represented by the black dots in B. Note the y axis is a logarithmic scale. The correlation has an $r^2=0.66$.

(UPDRS III and AIMS) were confirmed in this larger population. Because the PKG does not report tremor, the tremor scores were removed from the UPDRS III. As previously noted, asymmetric PD does not correlate well with the UPDRS III. This is most likely because the UPDRS III measures both sides, whereas the PKG scores measure only the most affected hand and thus will be relatively larger than the UPDRS III in asymmetric compared to symmetric disease and a doubling of the UPDRS-T score would bring these points closer to the linear confidence intervals. The exceptions are the very low BKS^{>50} scores, raising the question as to whether the relationship between the BKS^{>50} and the median BKS are truly linear and whether at the very high and very low levels of bradykinesia the scores show as much concordance. The capacity for the PKG to detect newly diagnosed PD suggests that it is sensitive at low levels of bradykinesia but it should also be recalled that the clinical scales are

not likely to be linear either. It should also be noted that the PKG measures distal bradykinesia and so patients with predominantly axial or lower limb bradykinesia are more likely to appear as outliers on this type of plot. In the case of the correlation between the PKG scores and AIMS, 9/11 outliers had lower DKS>75 than would be expected from their AIMS. The most likely explanation is that these are participants whose dyskinesia increases when under scrutiny (e.g. when being examined) and is thus higher than when they are at home undertaking usual activities. The requirement for a median DKS to be plotted with a log scale to obtain a linear correlation with AIMS and the distribution of DKS (Supplementary Figure), implies that error rate found in DKS should be expressed as $\text{Log}_{10}(\text{DKS})$.

Apart from the issue relating to subjects with recently diagnosed PD discussed above, the presence of outliers in both the BKS and DKS raise several possibilities. The first is that a device worn on the wrist may not capture clinical



Supplementary Figure

Figure A is a cumulative frequency histogram of the BKS for a single day of a normal subject (green bars) and bradykinetic subject (blue bars). At the top of the graph, the horizontal line shows the interquartile range and median (circle) for the normal (green line) and bradykinetic subject (blue line). There were 191 BKS epochs recorded from the bradykinetic subject and only 9 (5%) of these were greater than the median of the control subjects: thus the $BKS^{>50}$ was 9%. Note that the x axis has been cut to 60 for a better demonstration of the data and so several high BKS scores have been removed especially for the bradykinetic subject although these do not exceed 80 BK.

Figure B is a cumulative frequency histogram of the DKS for a single day of a normal subject (green bars) and dyskinetic subject (red bars). At the top of the graph, the horizontal line shows the interquartile range and median (circle) for the normal (green line) and dyskinetic subject (red line). There were 262 BKS epochs recorded from the dyskinetic subject and 213 (81%) of these were greater than the 75th percentile of the control subjects: thus the $DKS^{>75}$ was 81%. Note that the x axis has been cut to 60 for a better demonstration of the data and so 45 high DKS scores >60 have been removed from the dyskinetic subject's graph.

deficits cause by lower limb, truncal or facial abnormality. While the simplicity of wearing a single device increases patient acceptance and compliance it is clearly traded off against the inability to capture the problems of those patients whose scores are predominantly for other parts and do not affect the hand. It may equally be that some of the discordance is because the clinical rating scales done at a point in time either over or underestimate the clinical severity as capture by a more continual assessment.

In summary, the PKG's measures of bradykinesia and dyskinesia correlates with relevant clinical scales and can also capture the effect of therapeutic interventions. The standard error of the BKS asymptoted after 5 days of recording, implying that there is repeat reliability in the recording. We propose therefore that the PKG has a contribution to make as a consistent, valid and reliable measure of bradykinesia and dyskinesia.

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