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Research Report

An Ambulatory Tremor Score for Parkinson's Disease

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Abstract.
Background: While tremor in Parkinson's Disease (PD) can be characterised in the consulting room, its relationship to treatment and fluctuations can be clinically helpful.
Objective: To develop an ambulatory assessment of tremor of PD.
Methods: Accelerometry data was collected using the Parkinson's KinetiGraph System (PKG, Global Kinetics). An algorithm was developed, which could successfully distinguish been subjects with a resting or postural tremor that involved the wrist whose frequency was greater than 3 Hz. Percent of time that tremor was present (PTT) between 09 : 00 and 18 : 00 was calculated.
Results: This algorithm was applied to 85 people with PD who had been assessed clinically for the presence and nature of tremor. The Sensitivity and Selectivity of a PTT $\geq$0.8% was 92.5% and 92.9% in identifying tremor, providing that the tremor was not a fine kinetic and postural tremor or was not in the upper limb. A PTT >1% provide high likely hood of the presence of clinical meaningful tremor. These cut-offs were retested on a second cohort ($n = 87$) with a similar outcome. The Sensitivity and Selectivity of the combined group was 88.7% and 89.5% respectively. Using the PTT, 50% of 22 newly diagnosed patients had a PTT >1.0%.

The PKG's simultaneous bradykinesia scores was used to find a threshold for the emergence of tremor. Tremor produced artefactual increase in the PKG's dyskinesia score in 1% of this sample.
Conclusions: We propose this as a means of assessing the presence of tremor and its relationship to bradykinesia.

Keywords: Tremor, Parkinson disease, ambulatory monitoring, tremor dominant Parkinsons

INTRODUCTION

Tremor is common in Parkinson's disease (PD) and often leads to patients present for clinical advice. It occurs in approximately 75% of people with PD (PwP) [1]. Several forms of tremor are associated with PD [2, 3]. The classic asymmetric, resting tremor of PD has a frequency of 4–6 Hz, is inhibited by movement and may re-emerge with posture. There is also a postural/kinetic tremor that is 1.5 Hz greater than the rest tremor [4]. There are also other postural and kinetic tremors in PD whose frequencies are between 4–9 Hz [4].

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As there is no gold standard for identifying tremor or for distinguishing between normal and the various forms of abnormal tremor [5], examination by an experienced clinician is still the best diagnostic tool [3, 6]. However, diagnosis is only part of the clinician's problem. The literature is not explicit regarding the effect of treatment on PD tremor [7], but it does not always respond as well as other motor components to treatment [7–9]. In those that do respond, the tremor variably presents throughout the course of the day. As well, there is a tendency for patients to confuse tremor and dyskinesia. Thus there is an interest in knowing the amount of time spent with tremor, its relationship to the consumption of levodopa and the effect of treatment. This would require ambulatory monitoring to measure the presence of a known tremor over at least a day while the subject went about their usual activities.

There are numerous examples of the use of accelerometry to analyse the tremor of PD, especially with the advent of easily accessible, high quality accelerometers in smart phones [10–14] and well established tremor detection algorithms [15, 16]. We have described an accelerometer-based system for automated assessment of dyskinesia and bradykinesia [9]. This system has two algorithms, that every two minutes, provides a score of the likelihood of movements being either dyskinetic or bradykinetic (dyskinesia score (DKS) and bradykinesia score (BKS)) respectively. As a result, even the movement of subjects without PD (non-PD subjects) can have BKS and DKS and these scores will have a mean and distribution. A patient with PD is assessed by comparing the extent to which the mean and distribution of their scores deviated from those of non-PD subjects. This system also provides reminders to the patients to take L-dopa or other medications with a short duration effect and also measures patient registered acknowledgement of consumption of these medications. This system is now commercially available as The Parkinson's KinetiGraph [9] (PKG, Global Kinetics Australia) and has the potential to identify the presence of clinically diagnosed tremor and correlate its appearance with the consumption of medications, bradykinesia and dyskinesia. In reviewing previous publications relating to tremor, many were designed to detect tremor "on the fly" rather than *post hoc*. Thus the challenge of distinguishing between tremor and other repetitive movements (e.g. teeth cleaning) with high selectivity and sensitivity is much easier and the value of recording over long periods is that brief activities such as these can be accounted for by their scarcity compared to the tremor.

The aim of this study was to develop and validate this method of identify the presence of a previously identified tremor and to provide preliminary insights into its utility.

METHODS

Subjects

All assessments, including the use of the Parkinson's KinetiGraph (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 (Approval Number: QA 072-14) to review the medical records of patients whose data was used in this paper. The committee gave approval as a quality assurance study and waived the need for written informed consent from the participants. Records and information was made anonymous and de-identified prior to analysis. In total data from 194 records of people with idiopathic levodopa responsive PD and 28 control subjects were examined. All subjects had idiopathic PD according to the UK brain bank criteria and all had unequivocal bradykinesia. The average age of PwP was 66 years (SD $\pm$ 7.6 years), with on average, 7.1 years duration of disease and 48% were female.

The PKG system

The Parkinson's KinetiGraph data logger (PKG, Global Kinetics Australia) was used for recording bradykinesia and dyskinesia [17]. This logger is worn on the most severely affected wrist by PwP and contains a triaxial accelerometer and memory sufficient for >10 days of continuous recording. In this study the PKG was worn for at least 6 days. When recording was completed, data was downloaded and analysed by proprietary algorithms that calculate a bradykinesia score (BKS) and a dyskinesia score (DKS) [17]. The algorithm produces BKS and DKS every two minutes and the median of these scores from the period between 09 : 00–18 : 00 from all recording days correlates with the UPDRS III score (in the case of BKS) and the Abnormal Involuntary Movement Score (AIMS), in the case of the DKS [17]. The PKG logger uses a capacitive sensor to detect whether the logger is being worn (off-wrist). Please refer to Supplementary Figure 1 for details of the PKG.

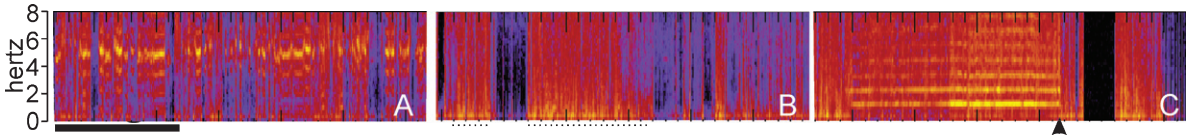

Fig. 1. Spectrograms power showing frequency according the Y axis (left with power according to a heat scale. Time is on the X axis (the bar indicates 20 mins). (A) a spectrogram from a subject with intermittent ~5 Hz tremor. (B) a spectrogram from a subject with dyskinesia (above dotted line) – not the broad frequency range. (C) a spectrogram of a subject running: note the frequency bands at 1.25, 2.25, 3.5, 4.5, 5.5 and 7 Hz. The dominant peak was either 1.25 or 2.25 Hz. Note that these bands stopped abruptly coinciding with ceasing running (arrow head).

Tremor analyses

The accelerometry data from the 6 day recording period was sampled at 50 Hz and processed through a 250 sample sliding window in steps of 1 s. A Hann function and Fourier transform were applied to each window to produce a frequency domain time series with a 1 second period, 0.2 Hz spectral resolution and units of dB mg^2 (i.e. 0 dB = 0.0098 m/s mg^2, 60 dB = 9.8 m/s mg^2).

The largest spectral peak above 1 Hz within each 1 second step was identified. Tremor was identified when the following criteria were met in at least 10 consecutive steps (i.e. 10 seconds):

- the peak spectral power in each step was >6 dB larger than the spectral median between 1 Hz and 10 Hz, and
- the frequency of the spectral peak in each step was between 2.8 Hz and 10 Hz, and
- the frequency of the spectral peak in a step differed from the frequency of the spectral peak in the two immediately adjacent steps by no more than 0.4 Hz/s.

Note that when a 1 second step had no spectral component above 6 dB that step was treated "immobile": i.e. the logger and the person wearing it had not moved in that second. Percent of time that tremor was present (PTT) was calculated as the percentage of time between 09 : 00 and 18 : 00 where tremor was identified, having excluded any period that was immobile (as defined above) or where the logger was not being worn.

Clinical assessment of tremor.

Clinical assessment of tremor distinguished between resting, postural and kinetic tremors as per the Unified Parkinson's Disease Rating Scale part III (UPDRS III).

RESULTS

Development of a tremor algorithm

Spectrograms were made from accelerometry recorded from the wrist of controls and PwP with and without tremor. By simple inspection, the clinical presence or absence of resting tremor was usually obvious and dominant peaks greater than 3 Hz were also obvious on the spectrogram although sub-harmonics were apparent (Fig. 1). Dyskinesia produced energy across a broad range of frequencies from 0.1–8 Hz, usually without a clear peak (Fig. 1B). The dominant peak from walking and running was usually less than 3 Hz (Fig. 1C).

Development and validation of a tremor algorithm

A tremor algorithm was developed by asking PwP and normal healthy controls without PD to wear the PKG in the laboratory while they were videoed performing a routine, including walking, pouring water from a jug into a row of 7 cups and repetitive movements high frequency movements (that might generate "tremor" artefact). In this part of the study, PwP were selected because they were either known to have resting or postural tremor that affected the wrist or because tremor was absent. The video allowed direct observation of the hand for tremor and correlation with the accelerometry trace. From this data a method of detecting the proportion of time that the tremor was present (PTT: Proportion of Tremor Time) was developed. In brief (see methods for full description), the largest spectral peak between 2.8 Hz and 10 Hz that lasted at least 10 seconds, whose frequency varied no more than 0.4 Hz/s between adjacent seconds was selected. Because the upper frequency of walking frequency is around 1.6 Hz [18, 19] and for running is typical around 2.2 Hz, whereas the resting tremor of PD is typically 4–6 Hz [4, 20], we required peaks to be greater than 2.8 Hz for tremor detection.

In these short studies, all subjects generated spectral peaks between 2.8 Hz and 10 Hz, lasting at least 10 seconds, and whose frequency varied no more than 0.4 Hz/s between adjacent seconds. However the proportion of tremor time (PTT) was brief except in those with resting tremor or postural tremor affecting the wrist. Some subjects with postural or kinetic tremors (including some subjects without PD) had a low PTT. In these cases the tremor did not significantly affect the wrist (e.g. confined to the fingers). Thus only subjects with resting or postural tremor affecting the wrist were deemed to have tremor for the purpose of this study (see further below) and the term "tremor" will be used to cover both types of tremor.

To assess the timing of tremor in an ambulatory at home setting, the PTT was calculated using the method above, for the period between 09 : 00–18 : 00, excluding periods of immobility (a surrogate for sleep [21]) or when the device was not worn. This was then validated in an ambulatory setting.

Validation of the algorithm in the ambulatory setting

PKGs ($n = 172$) performed in the 6 months prior to this study on PwP who attended the St. Vincent's Hospital Movement Disorder Clinic were known to either have tremor (*T*+) or not have tremor (T–) on the basis of examination, UPDRS III scores and history. These were divided into two cohorts – a test cohort (Cohort 1: $n = 85$) to establish the PTT thresholds for the presence of tremor and a re-test cohort (Cohort 2: $n = 87$) to confirm the findings of the previous cohort. There were 10 PwP who had tremor on UDPRS-III or history but had low PTT. These subjects had fine amplitude kinetic or postural tremor that did not have significant energy around the wrist that wore the PKG. A further 4 PwP had tremor but it did not affect the upper limb on which the PKG was worn. These 14 PwP were called T– for this analysis. A receiver operator curve (ROC) was performed to find the score that discriminated between T+ and T– with the greatest selectivity and sensitivity (Table 1). This PTT was 0.8% with a selectivity and sensitivity of 92.5% and 92.9% respectively (AUC = 0.92). However in the region between 0.6% and 1.0%, scores did not clearly distinguish between the T + and T– state (high false positive rate: Table 1) so this was called the "Grey Zone". Thus a PTT >1% was accurate in predicting tremor with 8.8% false positives and in predicting the absence of tremor when the PTT <0.6% with 8.1% false negatives (Table 1).

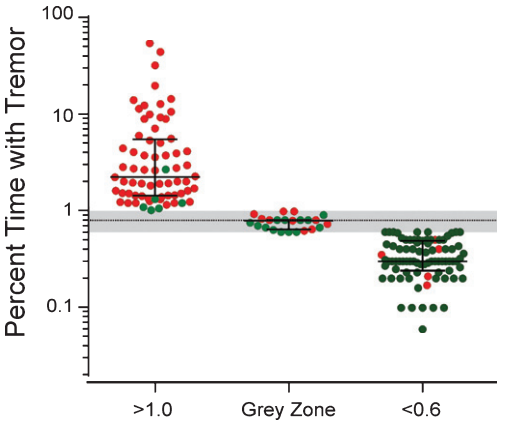

Fig. 2. A Graph showing subjects with tremor (Green dots: T+) and without Tremor (Red dots: T–) arranged into cohorts whose PTT were greater than 1%, in the Grey Zone or below 0.6%. The Y axis is the Percent Time with Tremor (with a logarithmic scale).

The PKGs in Cohort 2 ($n = 87$) were examined using the same criteria and method. Once again subjects with fine kinetic tremor or tremor not affecting the upper limb were classed as T–. Using an ROC, a PTT of 0.8% again provided the greatest selectivity and sensitivity (90.3 and 92.7 respectively: AUC = 0.96). The false negative and positive rates were similar to cohort 1 (see Table 1). The data was then pooled (Fig. 2 and Table 1). The ROC, using a PTT of 0.8% as the cut-off, provided a selectivity and sensitivity of 88.7 and 89.5 respectively for T+ and T–(AUC = 0.95). A PKG was performed on 22 newly diagnosed but untreated PwP. Fifty percent had a PTT >1.0 and 54% had a PTT >0.8.

The association between Tremor and Bradykinesia scores

The aim of this study was to develop a technique that revealed the timing of tremor with respect to medication, bradykinesia, and dyskinesia in an ambulatory at-home setting. The presence of the reminder and acknowledgment system on the PKG as well as bradykinesia and dyskinesia scores allowed for an examination of this possibility. A typical example is shown in Figs. 3 and 4 (and also Supplementary Figure 1 for an explanation of the PKG). As expected, the tremor tends to be present when the bradykinesia is increased (BKS is higher) than when it is low and in this subject, tremor is present when the BKS is higher than ~26. There is little relationship between "tremor positive" epochs and high DKS, suggesting that these are not simply a consequence of low frequency tremor

Table 1
Sensitivity and specificty of the tremor score

	cut off	N	False pos	False neg	Sensitivity	Selectivity
Cohort 1		85	14%	2%	92.5%	92.9%
	>1%	34	9%	–		
	0.6%–1.0%	14	21%	7%		
	≤0.6%	37	–	8%		
Cohort 2		87	19%	10%	90.3	92.7
	>1%	31	10	–		
	0.6%–1.0%	9	–	21%		
	<0.6%	47	4%	–		
Combined Cohort		172	9%	11.3%	88.7	89.5
	>1%	68	9	–		
	0.6%–1.0%	24	16%	25%		
	<0.6%	83	6%	–		

The top row of each cohort shows the number of number of PKGs, false positive and false negative rate and Sensitivity and Selectivity using a 0.8% as the divide between T+ and T–PKG's. The next 3 columns of each cohort show the Number and false positive and false negative rate in each band of PTT.

harmonics causing energy below 3 Hz and artificial elevation of the DKS. Each of these impressions can be more formally tested.

The BKS threshold for emergence of tremor

Tremor mostly commonly occurs as part of the "Off" state, when bradykinesia is present. Thus 2 minute epochs that have tremor should be more likely to be associated with a high BKS than with a low BKS. To test this, for each patient with a PTT >1.0%, epochs between 09 : 00–18 : 00 were sorted into those with tremor present (T+) or absent (T-) and a ROC was performed to find the BKS value that gave the optimal selectivity and sensitivity: in effect the BKS value where the subject switches from being T+ to T- (referred to as the tremor threshold). The median tremor threshold was a BKS of 27 (Fig. 5). If these BKS do represent a threshold, then lowering the BKS below this threshold should eliminate tremor. This did prove to be the case (See Supplementary Figure 1 for an example).

Tremor thresholds below 20 or above 35 are shown in Fig. 4 but these are unreliable because tremor was either very prevalent (BKS >35) or rare (BKS <20) making the ROC less robust (see Discussion). Six of the 12 subjects whose tremor threshold was less than 20 BKS had too few tremulous epochs (compared to tremor negative epochs) to make a meaningful ROC with meaningful estimates of threshold. The remaining subjects had tremor dominant PD and so the threshold most likely were meaningful. Similarly, most of those whose threshold was BKS >35 had too few tremor negative epochs to provide a meaningful ROC and estimate of tremor threshold.

The effect of dyskinesia on tremor score

The algorithm for calculating the DKS is strongly influenced by energy in frequencies under 3 Hz [17]. Thus it is relevant to know whether energy in low frequencies from tremor caused artefactual increase in the DKS. As a first step, in each case, DKS epochs were sorted into those that were T+ or T–. Using a similar rationale to the approach taken with the BKS threshold, the T+ epochs should have, on average, lower DKS than T- epochs. In most cases the median DKS was low (e.g. <4.0 in 60/83 cases) indicating that there was no dyskinesia. A ROC was not performed because the DKS was so low that a ratio had little meaning. In all 23 cases whose median DKS was higher than 4.0 (i.e. intermittent dyskinesia was present), the spectrograms were analysed and only one of these cases had high energy associated with tremor (Fig. 4B). In this case the tremor was of unusually low frequency with considerable energy in frequencies <3 Hz and thus likely to contribute to the DKS. Clinically, the patient does not have dyskinesia whereas in all the other cases dyskinesia was present and tremor occurred when dyskinesia was absent.

Thus the incidence of tremor contaminating the DKS in this series is approximately 1% of dyskinetic cases and 0.5% of all cases. We then examined the database held by GKC (the company that commercialises the PKG) for all 1085 PKGs with a median DKS >9 (equivalent to an AIMS of 10). This suggested that the incidence where there was a risk of tremor contaminating the DKS was ∼3% of cases in which significant dyskinesia was present. The characteristics of these cases was a high DKS, the PTT >5% and in half the BKS was high which would

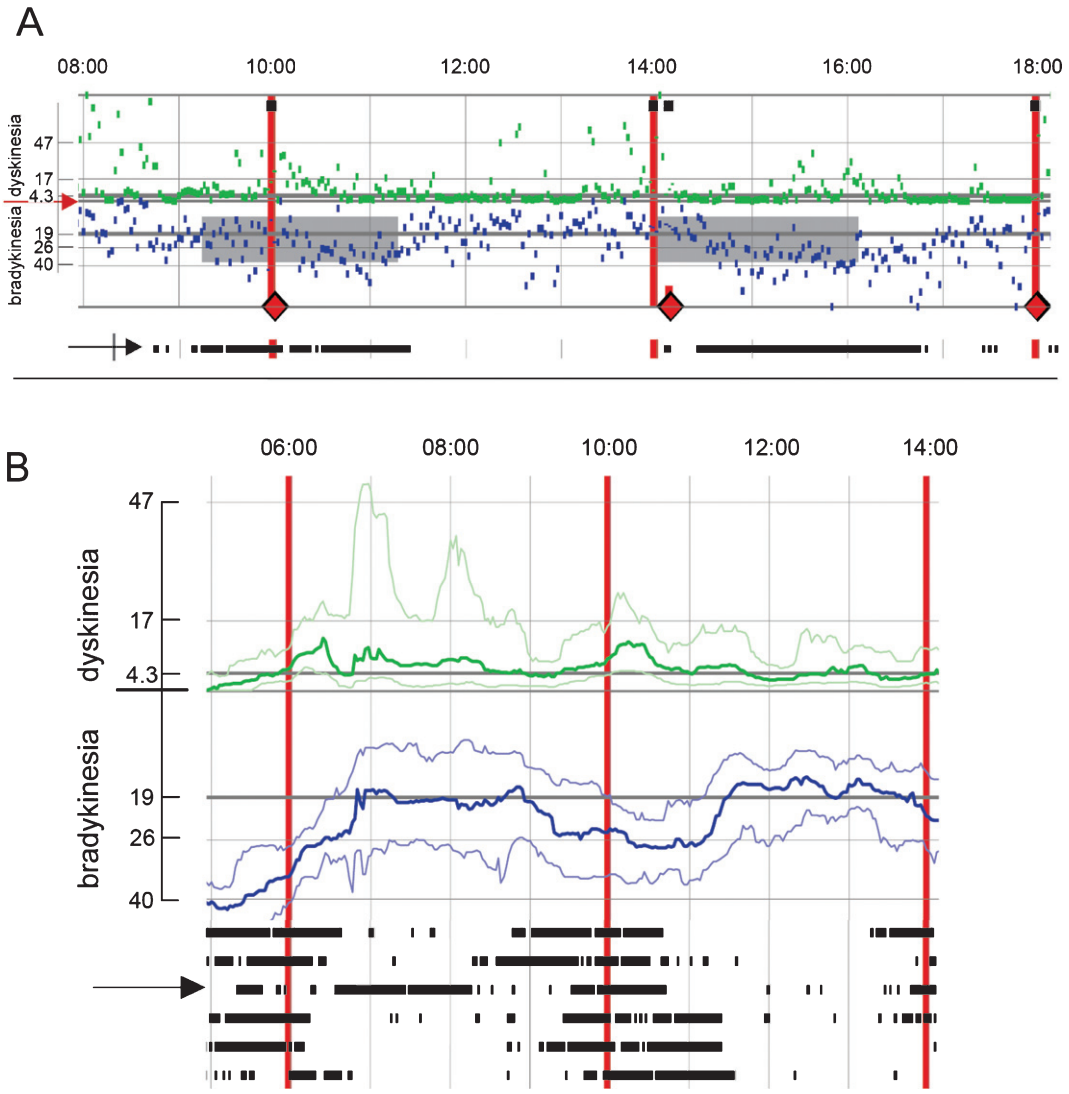

Fig. 3. (A) shows a fragment of the daily plot from the PKG (please see Supplementary Figure 1 for details of the PKG). Below it (black arrow) is the timing of "tremor positive" epochs (the tremor raster). These tend to correspond to the times when the blue dots were at or below the line corresponding to a BKS of 26 (UPDRS III ~25, shown as a grey shaded region). This day represents the second last day in Fig. 3B. (B) shows a fragment of the Summary plot from a PKG (please see Supplementary Figure 1 for details of the PKG). Figure 3A, was the 6th day of this PKG. This PKG shows a high BKS (i.e. is bradykinetic) at the time of medications at 6 : 00 and tremor is present prior at 06 : 00 on almost all days. The tremor tends to disappear as the median BKS pass below the line showing the BKS = 26 (about 30 minutes after the dose). Tremor tends to reappear about the time that the BKS begins to rise again (around 09 : 00) and variably disappear as the BKS falls again after the dose. Note that "wearing-off" as indicated by the emergence of tremor begins at different times each day (between 8 : 20-9 : 45). The dose appears to fail on one day (adjacent to the arrow) and there is variable delay in the response to 10 : 00 medications as judged by the time taken for tremor to disappear.

be unexpected in some with a very high amount of dyskinesia.

DISCUSSION

While an asymmetric, resting tremor with a 4–6 Hz frequency is typical of PD, there are also postural and kinetic tremors [2–4]. These various tremors of PD can be usually be diagnosed and distinguished from other types of tremor by examination, although laboratory assessment has been useful as a research tool [2–4]. For our intended purpose, it was assumed that the clinician can directly assess tremor frequency amplitude and the body locations that are involved, whereas it can be helpful to know historically the temporal pattern of tremor, especially in relation

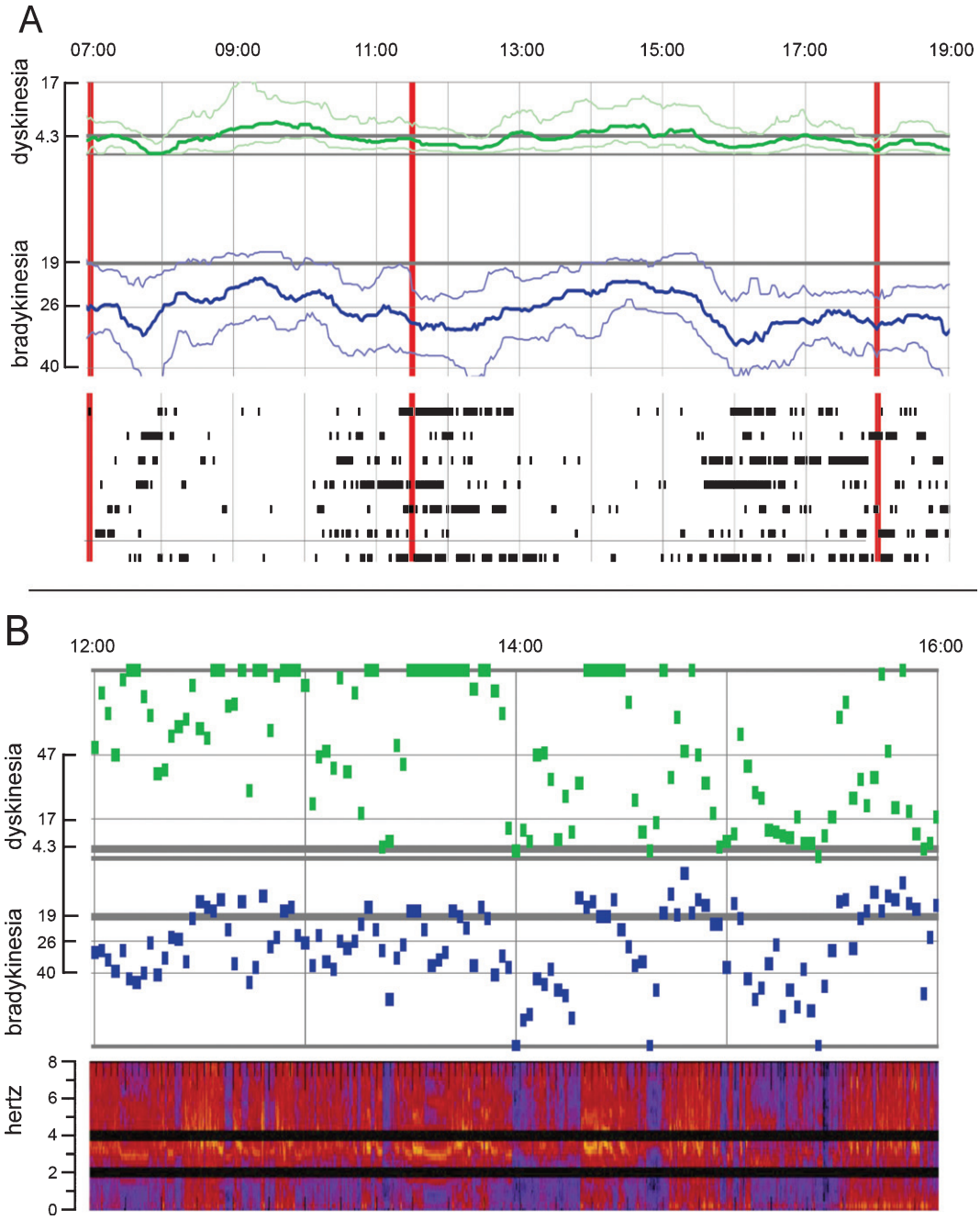

Fig. 4. (A) A PKG showing the Summary Plot (please see Supplementary Figure 1 for details of the PKG). It shows that tremor tends to occur when the BKS is higher than 26. On the other hand the DKS is usually higher than the median of normal subjects (DKS = 4.3) at periods when the tremor is absent. (B) The daily plot of a PKG from between 12 : 00-16 : 00 (please see Supplementary Figure 1 for details of the PKG). It shows that the BKS is high (a BKS of ~26) around 13 : 00, yet the DKS is also very high and hitting the upper limit. Examination of the Spectrogram showed a continuous tremor whose peak was at or under 3 Hz but with considerable energy at frequencies lower than the peak. This was producing energy in the range used to estimate dyskinesia.

to medications. For example, a history that tremor emerges when medications are due can be helpful in recognising "wearing-off" but requires the PwP to have accurate recall and the ability to distinguish tremor from dyskinesia. Our focus has been rest tremor because knowledge of its temporal pattern and response to therapy is clinically most relevant and because many of the kinetic and postural tremors

had insufficient energy at the wrist to provide useful signal in this system.

An important source of artefact in these analyses came from physical activity such as running or other physiological or mechanically driven activity of the wrist at frequencies above 3 Hz. Even though running is seldom at this frequency, some harmonics can be stronger than the running frequency and produce this artefact. Even so, these activities were not sufficiently protracted over the course of several days to provide a PTT of more than 0.8%. None of the PwP in this study ran at sufficient speed or frequency to produce tremor artefact although some of the control non-PD subjects did. The method described in this study is likely to underestimate the time with tremor time because tremor of very similar frequency had to be present for ten consecutive seconds for that time to be deemed as "tremor positive". Thus, changes in frequency by damping would reduce the estimated duration of an episode of tremor. While this may result in systematic underestimation of the precise duration of tremor each day, it does not affect the analyses for the purpose of assessing the timing of tremor with respect to medications or comparison between patients. The time with tremor will be particularly underestimated in a subject whose dominant tremor frequency is close to 3 Hz or has particularly strong sub harmonics below 3 Hz. In these cases, damping (for example by placing the hand on the knee) could potentially result in quite long periods where the dominant energy is below 3 Hz and thus that passage of tremor would not be accounted for in estimating PTT. Not only do these cases affect estimates of the time with tremor but also result in increased energy in the frequency range used by the PKG algorithms to estimate the DKS. It would seem however that this problem is infrequent (∼3% of all cases where dyskinesia is present) and can be readily recognised by the pattern of a high bradykinesia score, the presence of tremor and a high DKS: in itself a clinically unlikely pattern.

Postural and kinetic tremors of the upper limb typically affected the digits with little energy in the wrist. They failed to produce 10 concurrent seconds of consistent frequency to qualify as "tremor positive" according to our criteria. We did not include them as clinical case of "tremor" for the purpose of validating the method. As well, tremors that did not affect the upper limb (e.g. tremor of the lower limb, head or face) were also removed as they would not be detected by a wrist logger: there were only four cases that did not affect the upper limb. Interestingly, two cases with tremors of the lower limb, did cause

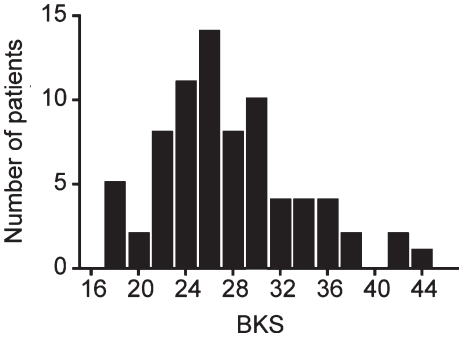

Fig. 5. A histogram showing the BKS threshold (as described in the text). The median BKS was 27.

qualifying "tremor signal" in the upper limb when the hands rested on the knees. While this study has focussed on the resting and postural tremor of PD that affects the wrist, it is likely that Essential Tremor affecting the wrist would also be captured.

Any two minute epoch is described as "tremor positive" if that epoch had at least 10 seconds of tremor: thus the graphic representation (e.g. Fig. 3) may appear to have more time with tremor than the PTT. The concept of a "tremor positive" BKS and DKS epoch does allow for both validation and some insights into the level of bradykinesia at which tremor emerges. In terms of validation, it would be expected that bradykinesia would be more severe (represented by a higher BKS) when tremor is present and less severe (lower BKS) when tremor is absent. In considering this, it should be noted that only 10 of the 120 seconds in a 2 minute tremor positive epoch needs be tremulous whereas the whole 2 minutes is used to derive the BKS. Thus a perfect correspondence is unlikely but nevertheless ROCs with respectable sensitivity and selectivity were generated. Furthermore they produced thresholds for the emergence of tremor that is consistent with clinical experience (a BKS of 27 relates to a UPDRS III in the mid to high 20 s). It also concords with clinical experience that tremor can accompany varying severities of bradykinesia and this study suggests that while the median is a BKS of 27, the range is quite wide. Many of the very low thresholds (BKS <18) and very high thresholds (BKS <35) are likely to be statistical artefacts. The ROC test depends on ratios and is most robust when there are roughly equal proportions of tremor positive and tremor negative cases. However when the BKS is low there are very few tremor positive BKS and when very high there are few tremor negative BKS. Nevertheless, some cases with a BKS threshold of 18–20 (corresponding to a UPDRS III of 0–15) do represent

cases of tremor dominant PD. A further confirmation of the validity of this tremor was the frequency of tremor in newly diagnosed subjects.

The advantage if continuous recording of tremor in relationship to a record of bradykinesia and medication consumption means that the emergence of tremor can more readily linked to "off " periods and the "threshold of bradykinesia associated with emergence of tremor can be established (as described here) and aid in the quantification of tremor dominance. Furthermore it aids in untangling the confusion that some patients have between tremor and dyskinesia. We propose the method of representing tremor discussed here has the potential to be a practical clinical tool in conjunction with the other scores presented by the PKG in the management of PD. Further studies and practical use of this tool in clinical practice will confirm whether this is the case. With further study the BKS Threshold may also lead to further insights into the relationship between bradykinesia and tremor [2].

CONFLICT OF INTEREST

Sam O'Connor and Philip Churchward are employed by, and have equity in Global Kinetics Corporation (GKC). Malcolm Horne has equity in GKC. Michelle Braybrook and Parisa Farzanehfar are supported by a grant provided by GKC to the Florey Institute.

SUPPLEMENTARY MATERIAL

The supplementary information is available in the electronic version of this article: http://dx.doi.org/10.3233/JPD-160898.

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