A Method for Measuring Time Spent in Bradykinesia and Dyskinesia in People With Parkinson's Disease Using an Ambulatory Monitor

Hamid Khodakarami
UiB Global
Navid Shokouhi
Global Kinetics
Malcolm Horne (malcolm.horne@florey.edu.au)
The Florey Institute of Neuroscience and Mental Health https://orcid.org/0000-0001-9427-2100

Research

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Abstract

Background

Fluctuations in motor function in Parkinson's Disease (PD) are frequent and cause significant disability. Frequently device assisted therapies are required to treat them. Currently, fluctuations are self-reported through diaries and history yet frequently people with PD do not accurately identify and report fluctuations. As the management of fluctuations and the outcomes of many clinical trials depend on accurately measuring fluctuations a means of objectively measuring time spent with bradykinesia or dyskinesia would be important. The aim of this study was to present a system that uses wearable sensors to measure the percentage of time that bradykinesia or dyskinesia scores are above a target as a means for assessing levels of treatment and fluctuations in PD.

Methods

Data in a database of 228 people with Parkinson's Disease and 157 control subjects, who had worn the Parkinsons Kinetigraph ((PKG, Global Kinetics Corporation^{TM}, Australia) and scores from the Unified Parkinsons Disease Rating Scale (UPDRS) and other clinic scales were used. The PKG's provided score for bradykinesia and dyskinesia every two minutes and these were compared to a previously established target range representing a UPDRS III score of 35. The proportion of these scores above target over the 6days that the PKG was worn were used to derive the percent time in bradykinesia (PTB) and percent time in dyskinesia (PTD). As well, a previously describe algorithm for estimating the amplitude of the levodopa response was used to determine whether a subject was a fluctuator or non-fluctuator.

Results

Using this approach, a normal range of PTB and PTD based on Control subject was developed. The level of PTB and PTD experienced by people with PD was compared with their levels of fluctuation. There was a correlation (Pearsons ρ=0.4) between UPDRS II scores and PTB: the correlation between Parkinson Disease Questionnaire scores and UPDRS Total scores and PTB and slightly lower. PTB and PTD fell in response to treatment for bradykinesia or dyskinesia (respectively) with greater sensitivity than clinical scales.

Conclusions

This approach provides an objective assessment of the severity of fluctuations in Parkinsons Disease that could readily easily be used in routine care and in clinical trials.

Introduction

The first few years of Parkinson's Disease (PD) respond well to levodopa and other dopaminergic medications (1, 2). However, the duration of symptomatic benefit derived from each dose of levodopa gradually shortens, plateauing at about 3 hours. After 2 years of disease, ~50% of people with PD (PwP)

are symptomatically aware of this shortening of benefit and ~70% of PwP eventually experience this effect (3). Historically, this phenomenon was considered a transition from mobility (“on”) to bradykinesia (“off”) and referred to as “wearing-off” (4). However treating clinicians are frequently unaware of the presence of “wearing-off”, (5, 6) because PwP do not always recognise the accompanying symptomatology as re-emergence of bradykinesia (7-9) and may perceive them as a transitions to non-motor symptomologies (9-11).

Implicitly, “wearing-off” is preceded by a response to levodopa and typically occurs 3-4 hours after that response. These “off-on-off” transitions will be referred to as fluctuations and dyskinesia will be considered as a separate entity, despite similar underlying mechanisms and frequent co-occurrence (3). Specifically, the term fluctuator will apply when there is a significant Levodopa Response (LR) and thus the potential for significant “wearing-off”.

In PD, routine clinical care and clinical trials depend on self-reporting of fluctuations (8, 12, 13), but as noted above, fluctuations are often not recognised by the PwP. However, objective measurement of PD using wearable devices is now possible (14) and may be superior to motor diaries in detecting the presence and timing of fluctuations and dyskinesia (6) and leads to better outcomes when used in the management of PD (15, 16). There are, however, important conceptual differences between self-reporting (such as by diary) and objective measurement of fluctuations and dyskinesia.

To report fluctuations, PwP must implicitly be aware of fluctuations. Thus, the diary or history report the *symptoms* or conscious experience of the PwP, whereas objective measures of bradykinesia, including the Unified Parkinsons Disease Rating Scale (UPDRS) part III, measure the *signs* of bradykinesia. There are many examples in medicine, such as asthma (17), where patient’s assessment of function may differ from an objective measurement of function. Diaries require recognition of three states: “off”, *“*on”, and “dyskinesia”. PwP who can recognise these states vary in the level of bradykinesia that they recognise as transitioning from “off” to “on” (11). Similarly, the level that PwP recognise as the transition to dyskinesia varies from subject to subject. A previous study comparing diaries and objective measurement showed that patients whose levels of bradykinesia were habitually high tended to identify “off” at higher objective scores (18), possibly due to an altered self-awareness of motor states in PD (19). Objective measurements provide a continuous range of bradykinesia, with “off” referenced to a specific point on the scale, marking the boundary between acceptable and unacceptable or treatable bradykinesia. Thus, “off” time measured by diary records the hours the subject perceived medications to have failed, whereas objective measurement records the amount of time that scores were above an objective target. A diary records a *symptom* whereas objective measurement records a *sign*: these may be similar, but they are not identical.

It is difficult to find an example in medicine where objective measurement and effective therapy exist without there being defined targets for control. Marsden and Parkes noted similarities between PD and diabetes (20), a condition where measurement is routine and terms such as “targets” and “controlled” are used. Targets are derived from physiological norms, improved outcomes and health economics.

Achieving these targets comes with improved clinical outcomes, recognising that it is not always possible to achieve the target. Targets help avoid unnecessary treatments of those already "well controlled" and focus attention on those who would benefit from change in therapy. A bradykinesia target would be a score on a bradykinesia scale marking the boundary between acceptable bradykinesia and bradykinesia that requires an intervention. The Parkinson's KinetiGraph (PKG, Global Kinetics Corporation^{TM}, Australia) is an objective measurement system where targets have been based on physiological norms (21, 22), expert opinion and the efficacy of these targets to guide therapy and improve outcomes (15, 16). This system was used in this study, although any objective system that assesses bradykinesia and dyskinesia during natural behaviours over a sufficiently protracted period and with a sampling frequency that captures fluctuations and dyskinesia following levodopa doses could be used.

This study examined the feasibility of measuring "time in bradykinesia", "time in dyskinesia", and identifying fluctuations using an objective ambulatory measurement of PD as a means for assessing levels of treatment and fluctuations in PD. The findings of this study suggest that this approach shows promise as an outcome measure in clinical trials of PD therapies and to guide the management of PD.

Methods

This is a study of a database collected in previous studies and approved by St Vincent's Hospital Melbourne Human Research and Ethics Committee. The criterion for selecting 228 PwP from this database was that contemporaneous scores from the UPDRS III and PKG data were available: 90% of whom also had the Parkinson's Disease Questionnaire (PDQ39) and the other three UPDRS scales. The clinical characteristics of the participants are shown in Table 1. Included are 84 PwP who participated in two previously reported studies (15, 16) where oral therapy was used to treat bradykinesia or where Deep Brain Stimulators or changes in oral therapy were used to reduce dyskinesia. Demographics and selection are described in the results sections and in Tables 1 and 5. Also included were 157 subjects aged over 60, recruited from bowls and golf clubs, University of the 3rd Age, and Probis who had no previous concern of neurodegenerative disorders or gait disorders requiring use of walking aids. These Controls subjects wore the PKG for 6 days, but no clinical scales are available. All studies were carried out in accordance with the guidelines issued by the *National Health and Medical Research Council of Australia* for Ethical Conduct in Human Research (2007, and updated May 2015) and in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Clinical characteristics of participating subjects and inclusion criteria into the analyses are discussed below.

Table 1 Demographics and clinical scores of participants

	PwP§	Controls§
Number	228	157
Gender	35% F: 65% M	61% F: 39% M
Age	71 (9.7)	69.6 (8.7)
Disease Duration	6.0 (6.0)	n/a
Unified Parkinsons Disease Rating Scale		
Part I	10.0 (8.0)	n/a
Part II	11.0 (9.0)	n/a
Part III (“ON”)	36.0 (18.0)	n/a
Part IV	4.5 (6.0)	n/a
Total	62.5 (29.3)	n/a
Levodopa Equivalent Daily Dose (LEDD)	675 (500)	n/a
Parkinsons Disease Questionnaire	28 (29)	n/a
median Dyskinesia Score (mDKS)	2.1 (3.7)	2.6 (2.8)
Adjusted median Dyskinesia Score	1.3 (2.5)	1.5 (2.2)
median Bradykinesia Score (mBKS)	25 (9.6)	22.0 (2.8)
Active median Bradykinesia score	23.9 (7.8)	21.4 (3.2)

§ Values are mean and standard deviation (in parenthesis) of each variable from PwP and Control subjects.

The PKG System

The PKG system consists of a wrist-worn data logger, a series of algorithms that produce data points for bradykinesia (23) and dyskinesia (23) every two minutes and a series of graphs and scores that synthesise this data into a clinically useful format known as the PKG. The PKG plots the two-minute bradykinesia and dyskinesia scores against the time of day and shows when medications are due. The numerical output is summarised in the Glossary that follows. The reader is referred to the company’s website for further details (http://www.globalkineticscorporation.com.au/) and to other publications (15, 23-28).

Glossary of PKG terms

The PKG system assumes that there is a continuum in the distribution of the kinematics from Controls to PwP and that with treatment, the kinematics of some PwP can be normalised. Consequently, Controls as well as PwP have bradykinesia and dyskinesia scores, and in PwP, these scores can enter the control range if treatment is optimal.

Bradykinesia Score: This is the bradykinesia score for each 2 minute epoch produced over all days that the PKG was worn (23).

Epoch: Each 2-minute period of recording is called an epoch and analysed as previously described (23). The following scores are estimated from the part of the day between 09:00-18:00, excluding epochs where the logger senses that it was not being worn, or the Bradykinesia Score≥80 (usually sleep (25, 27)). As well, *inactivity* is removed for some scores. Inactivity is when so few movements are made over 2 minutes that clinical assessment of bradykinesia would not be possible and identified when the 30 minutes centre weighted moving median bradykinesia score is greater than 40. *Available epochs* are epochs remaining after those related to inactivity, sleep or occurring when the logger is not worn have been removed.

Median Bradykinesia Score (mBKS): The mBKS is the 50th percentile of all bradykinesia scores from epochs between 09:00 and 18:00, when the logger was worn and bradykinesia score≤80, over all available days that the PKG was worn (usually 6 days)(23).

Active median Bradykinesia Score. This is the 50th percentile of the bradykinesia score for all from epochs over days that the PKG was worn (usually 6 days). As well, epochs with inactivity are removed: inactivity being when so few movements are made over 2 minutes that clinical assessment of bradykinesia would not be possible and identified when the 30 minutes centre weighted moving median bradykinesia score is greater than 40.

Percent time bradykinesia (PTB). This is explained below after reader is introduced to Severity Levels (below).

Dyskinesia Score: This is the dyskinesia score for each 2 minute epoch produced over all days that the PKG was worn (23).

Median Dyskinesia Score (mDKS): This is the 50th percentile of all dyskinesia scores from between 09:00 and 18:00, when the logger was worn and bradykinesia score≤80, from all days that the PKG was worn (23).

Adjusted median Dyskinesia Score. This is the 50th percentile of the available dyskinesia score for all days that the PKG was worn excluding those in which either walking or tremor were detected. Walking refers to maintained perambulation detected using a supervised gradient boosting decision tree model to identify walking levels with sufficient energy to influence the dyskinesia signal. This model used features obtained from conventional gait detection and from the pattern of harmonics of the acceleration signal

during the epoch under examination. Using a previously described tremor detector (26), epochs with tremor were also identified. Epochs with “walking” identified by the algorithm were removed as it is possible for dyskinesia and walking to occur in the same epoch and thus, these epochs are uninterpretable. If tremor was detected in the epoch *and* its dyskinesia score≥10, the epoch’s dyskinesia score was set to zero. The assumption was that under these circumstances the elevated dyskinesia score may have been mostly due to tremor, rather than dyskinesia. Epochs where bradykinesia score>80 or the logger was not worn were removed.

Percent time Dyskinesia (PTD). Percent time in dyskinesia (PTD) was estimated as the percent time of available epochs whose dyskinesia score≥10 *and* in which neither walking nor tremor were detected (as for Adjusted median Dyskinesia Score). The 75th percentile of the remaining epochs in the control population was 10, hence dyskinesia score≥10 was chosen as the threshold for PTD. PTD was estimated on available epochs between 09:00-18:00 on the 6 days the PKG was worn, and expressed as the percentage of all available epochs in that period. As the number of available epochs will vary from person to person, time in bradykinesia is expressed as a percentage, allowing comparison between subjects.

The first dose time. The PKG logger is programmed to vibrate at specific times to remind subjects to take their medications. Subjects can acknowledge when they consume the medications by “swiping” the smart screen on the watch. The first dose time is the 5 epochs (10 minutes), centred on the first reminder after 05:00.

Time of peak levodopa effect: This is the time when levodopa was estimated to have had its peak effect. It is calculated as the peak of the smoothed bradykinesia score time series from 46 minutes to 90 minutes after first dose time, using data from all recorded days (24).

Definition of Severity Levels of Bradykinesia

Severity Levels were fully described in a previous study describing how PKG data could be used to predict the absolute change in the UPDRS III produced by a levodopa challenge test (24). Here we briefly reiterate aspects of this model that are relevant to Severity Levels and a levodopa response (LR).

The UPDRS III scale was divided into six Severity Levels (Table 2 (29)) and the UPDRS III scores measured prior to and after the levodopa challenge were sorted into these six Levels. An algorithm assigned each PKG epoch to a Severity Level corresponding to the range of UPDRS III scores (Table 2). In the current study, this algorithm is used to measure the proportion of time a PwP is in bradykinesia and to measure Levodopa Response (LR). Note that the terms “Bradykinesia Severity Level” and “Severity Level” are used interchangeably, even though tremor and other information as well as the PKG’s bradykinesia scores were used in developing the score.

Table 2 PKG Severity Levels compared to UPDRS III

Target range	In target			Above target		
Bradykinesia Severity Level	0	1	2	3	4	5
UPDRS III Interval	0-10	10-22.5	22.5-35	35-47.5	47.5-60	≥ 60

This table shows the range of MDS-UPDRS III corresponding to each bradykinesia severity level. Epochs in Severity levels 0, 1 and 2 were in target, whereas those in level 3 or above were above target.

Targets

Bradykinesia is considered “in target” and “controlled” when “Severity Level<2.5” and “above target” and “uncontrolled” when the “Severity Level≥2.5” and a “significant” LR is when the Severity Level changes by ≥1.15. This is based on a previous study (24) that used data from clinical levodopa challenge tests to show that changes in Severity Level≥1.15 were clinically significant and indicated a response to levodopa. A Severity Level of 2.5 (i.e., the midpoint between levels 2 and 3 in Table 2) approximates an mBKS of 26 and a UPDRS III of 35 and an LR of 1.15 is equivalent to ~14-point reduction in the UPDRS. The performance of the model is affected if the sample of available epochs becomes too small. This results in increased variability, which is particularly relevant at the time of the first dose, because some subjects continue to sleep or are inactive at that time. Excess Variability is present when the standard deviation of Severity Levels is greater than one unit of Severity Level at the times of the first dose and Effect Time. Cases with excess variability (34%) were removed when estimating LR and other dependent estimates. This is relevant for the early morning period (time of first dose) because sleep and or inactivity was more common and because there was only a maximum of 30 epochs available in early morning periods over 6 days (see Early Morning bradykinesia score, below).

Definition of parameters that depend on estimates of Severity Levels

In Target or Controlled. This relates to when the Severity Level was below the target range (Severity Level <2.5 or bradykinesia score<26). The term “on” has been reserved for the subjective symptom of levodopa action observed by the PwP.

Out of Target or Uncontrolled. This relates to when the Severity Level was above the target range (Severity Level ≥2.5 or bradykinesia score≥26). The term “off” has been reserved for the subjective symptom of loss of levodopa action observed by the PwP.

Percent time bradykinesia (PTB). PTB was estimated as the percent time in Severity Levels 3, 4 and 5. PTB was the number of epochs (excluding inactivity, sleep and the logger not worn as per Active median bradykinesia score) in Severity Levels 3, 4 and 5 between 09:00-18:00 on the 6 days the PKG was worn, expressed as the percentage of all available epochs in that period. As the number of available epochs will

vary from person to person, time in bradykinesia is expressed as a percentage, allowing comparison between subjects.

Early Morning Bradykinesia Score: The Bradykinesia Severity Level estimated at the time of the first dose. This score was not estimated if there was no dose reminder or the first dose reminder was earlier than 05:00 or if more than 50% of the epochs were unavailable (24). Early Morning Bradykinesia was considered to be present when the Severity Level was≥2.5, in keeping with the definition of PTB.

The levodopa response (LR). The LR was estimated by calculating the magnitude of improvement in bradykinesia Severity Level at time of peak levodopa effect compared with first dose time (Fig. 1a). An improvement in Severity Level of 1.15 predicted an improvement of 14 UPDRS III points which also approximated a 30% improvement (24). We will use the terminology of “significant and non-significant” LR to refer to LR that are greater or less than 1.15 severity points, respectively.

Wearing-Off. If the LR declines by ≥1 Severity Levels within 2 hours of time of peak levodopa effect, it was defined as Wearing-Off (Fig. 1a). The rationale was to detect a decline in levodopa action occurring at ~3 hours from dose consumption.

Assessment of fluctuations

The LR is used to distinguish between *Fluctuators* (those whose LR is significant) and *Non-Fluctuators* (those whose LR is not significant) (Fig. 1b and Fig. 1c). Each were then divided as to whether their activity was in target (controlled) or out of target (uncontrolled). The abbreviations are provided here because they are also used in several of the Figures.

Non-Fluctuators-Controlled (NFC). These are PwP with a non-significant LR and whose early morning Bradykinesia level was already in the Controlled range (in target) prior to the first dose. Presumably, these would include PwP with early non fluctuating PD.

Non-Fluctuator-Uncontrolled (NFU). These are PwP with a non-significant LR not significant but whose early morning Bradykinesia level are in the Uncontrolled range (out of target). PwP with high bradykinesia and little or no LR are presumably undertreated or unresponsive to levodopa and indeed may have another akinetic-rigid syndrome.

Fluctuators: PwP whose response (LR) to the first morning levodopa dose was significant. However, this LR may not be large enough to cause bradykinesia scores to fall below target. In these circumstances, despite fluctuations, there is no reduction in the time spent in the target range (although bradykinesia scores are improved). As well, the LR might persist up to and beyond the next dose (no “wearing-off”) or there may be a rise in bradykinesia scores (“wearing-off”) prior to the next dose. Consider for example a PwP whose first morning dose significantly changes objectively measured scores (e.g., UPDRS III by 30 points) from being above target to below target 30 minutes later. The next dose is due in 5 hours, but after 3 hours in target, bradykinesia rises above target and remains high until the next dose 90 minutes

later (Fig. 1a). For the five hours between the first and second dose this PwP is above target 120 mins (30+90). The medication regimen is then changed to be 3 hourly: it still takes 30 mins following the first dose until target is reached but the subject now stays within target until the next dose (and possibly for the rest of the day). Both are fluctuators (recognised by the significant LR, Fig. 1b) but will be categorised separately. Similarly, subjects whose LR is significant but not sufficient to reach target are also recognised as a separate case. To accommodate these concepts four categories of fluctuators were recognised (Fig. 1b).

***F**luctuator whose response enters the **C**ontrolled range and **P**ersists in that range (FC_P)*. Early morning "off" with significant LR that results in bradykinesia levels that enter the target range and does not "wear-off".

***F**luctuator whose response enters the **C**ontrolled range, but the response **W**ears **O**FF (FC_{WO}).* Early morning "off" with significant LR that results in bradykinesia levels that enter the target range but the LR "wear-off".

***F**luctuator whose best response remains in the **U**ncontrolled range and **P**ersists in that range (FU_P).* Early morning "off" with significant LR but the bradykinesia levels remain above target but does not "wear-off".

***F**luctuator whose best response is in **U**ncontrolled range, but the response **W**ears **O**FF (FU_{WO}).* Early morning "off" with significant LR but the bradykinesia levels remain above target and "wear-off".

Clinical Scales

Clinical Scales were performed within a month or less of wearing the PKG. The UPDRS was the Movement Disorder Society version (MDS-UPDRS) and was performed during the day while participants were taking their usual medication. All MDS-UPDRS III scoring was done by St Vincent's Neurology Department staff who had received the MDS-UPDRS training.

Results

Percent Time in Bradykinesia (PTB) and Percent Time in Dyskinesia (PTD) were estimated using data from 228 PwP and 157 control subjects. The first step was to compare the distribution of PTB and PTD in controls and PwP to establish the normal range and the relationship to the PKG's median bradykinesia and dyskinesia scores (mBKS and mDKS). The next step was to examine the relationship between PTB and PTD and the various categories of fluctuators. Finally, the relationships between PTB, PTD and fluctuator category was compared to clinical scales and the response to treatment.

The distribution of PTB and PTD in Controls and PwP

The values of PKG parameters that separated PwP from controls were originally established by comparing data from subjects with and without PD, and similarly, it would be expected that the range of PTB and PTD values for controls will lower than the values found in PwP. Based on the distribution of PTB in Controls (Fig. 2a), the upper limit of the normal range was set to 30%. When the PTB of PwP and Control subjects were plotted against the median bradykinesia scores (mBKS, Fig. 2b), it was apparent that most PwP with an mBKS<23 were in this normal range. The box and whiskers plot for PTB of PwP whose mBKS<23 and ≥23 (Fig. 2a) confirms that almost all PwP with an mBKS≥23 have a high PTB (>30%). As the target for good control of PD is an mBKS is ≥26 (16), there are some PwP whose mBKS is in target (≥23 and <26) who have elevated PTB (shaded in Fig. 2b and discussed further below). Similarly, based on the distribution of PTD of Controls (Fig. 2a), the upper limit of PTD for Control subjects was set at 20%. Plotting the PTD of PwP and Control subjects against their median dyskinesia score (mDKS, Fig. 2c) shows that most subjects with an mDKS<5 are in this normal range for PTD. The box and whiskers plot for PTD of PwP whose mDKS<5 and ≥5 (Fig. 2a) confirms that almost all PwP with an mDKS≥5 have a high PTD (>20%). When the mDKS is above 7 (target), the PTD is almost always elevated.

The relationship between PTB and PTD was also examined (Fig. 2d). When PTD is elevated, PTB is almost always low, whereas when PTB≥30%, PTD is low. Only 3% of PwP have both high PTD and PTB: that is, dyskinesia with concomitant bradykinesia is uncommon in this cohort. Out of all PwP, 24% have PTD≥20% and 57% have PTB≥30% (Fig. 2d). Unless otherwise stated, further investigation of PTB will relate to PwP with mBKS≥23, and PTD will relate to either mDKS≥5 or to PTD>20%.

The relationship between Fluctuators, PTB, and PTD

A “Fluctuator” was defined in the Methods and Fig. 1c as a PwP who has a significant levodopa response (LR) (24), whereas PwP whose LR was non-significant are termed non-fluctuators with scores that are in target (controlled non-fluctuators or above target (uncontrolled non-fluctuators). Fluctuators were sorted into four further categories (Fig. 1 and Methods) based on whether the LR is enough to reduce the bradykinesia score into the target range (i.e., controlled fluctuator) or not (i.e., uncontrolled fluctuator) and whether the LR persisted until the next dose or “wears-off”. See Fig. 1 and Methods for full definitions of these four categories of Fluctuators.

Relationship between PTB, early morning bradykinesia and response to levodopa

The percentage of PwP with and without fluctuations at different levels of PTB was estimated (Fig. 3a and Table 3). As PwP with fluctuations frequently experience early morning bradykinesia, this was also estimated, along with the amplitude of the LR. Note that 34% of PKG were excluded from assessment because of sleep or inactivity at the time of the first dose (see Methods).

While PwP with a PTB in the normal range (<30%) were mostly controlled non-fluctuators, having neither a significant LR or early morning bradykinesia (Table 3), 40% were Fluctuators, most likely representing subjects whose LR brought their bradykinesia score into target where it stayed without "wearing-off" (i.e., FC_P in Fig. 1).

Fluctuators were the most frequent category when the PTB was between 30% and 75% with early morning bradykinesia in ~2/3 of cases. Many of these cases would have an mBKS between 23 and 26 and lie on the shaded area of Fig. 2b. Note that when the median bradykinesia score is exactly at target (i.e., mBKS=26), by definition, 50% of bradykinesia score are above target, implying that the bradykinesia scores is fluctuating above and below target (FC_{WO} in Fig. 1). Similarly, when mBKS lies between 23 and 26, there will be fluctuations above target, but to a lesser degree. When the PTB was high (≥75%), most cases were uncontrolled non-fluctuators and early morning bradykinesia was almost universal (96%). There may be several reasons that the LR was non-significant in ~2/3 of these cases, including undertreatment or non-responsive PD.

The difference in PTB of PwP in controlled non-fluctuators and uncontrolled non-fluctuators is shown again in Fig. 3b, which also shows that PTB of Fluctuators is intermediate (30%-~75%) between controlled and uncontrolled non-fluctuators. The Levodopa Equivalent Daily Dose (LEDD) was lower in non-fluctuators (median= 600, interquartile range 463) than in fluctuators (median=700, interquartile range 433), but this was not significant (p=0.43, Mann Whitney).

Table 3 The proportion of PwP with Early Morning bradykinesia or a significant LR according to PTB

PTB	Percent	EMB	LR	NFC	NFU	F
All	100%	80%	45%	19.7%	35.5%	44.8%
<30%	11.8%	33%	30%	54.2%	4.2%	41.7%
30%-75%	59.6%	72%	56%	21.5%	28.9%	49.6%
≥75%	28.6%	96%	32%	1.7%	62.1%	36.2%

The Percent Column shows percent of cases in each category of PTB. EMB (Early Morning Bradykinesia) column shows percent of cases in each category of PTB with Early Morning Bradykinesia ≥2.5 Severity Level. LR column shows percent of cases in each category of PTB with Significant Levodopa Response. Columns headed by NFC (Controlled Non-Fluctuators), NFU (Uncontrolled Non-Fluctuators) and F (Fluctuators) show the percent of each category of fluctuator in each PTB category. This Table should be read with Fig. 3a.

Relationship between PTB and various types of Fluctuators

The relationship between PTB and fluctuator subcategories (described above and Fig. 1b) was further examined in Fig. 3b. Fluctuators whose LR reached target (FC_P and FC_{WO} in Fig. 3b) had less PTB than those fluctuators whose LR did not reach target (FU_P and FU_{WO} in Fig. 3b). Fluctuator categories with “wearing-off” had higher PTB than associated category without “wearing-off” (Fig. 3b). It is difficult to discern a clear pattern in the Levodopa Equivalent Daily Dose values in Fig. 3b other than uncontrolled fluctuators with "wearing-off" (FU_{WO}) receive the lowest Levodopa Equivalent Daily Dose, presumably reflecting undertreatment or contraindications to treatment.

In PwP with PTD≥20% (Fig. 3c), 55% were Fluctuators and 32% were controlled non-fluctuators. Note that classification of fluctuators and “control” refers to bradykinesia (see Fig. 1) and not to whether or not dyskinesia was “controlled”. Most Fluctuators were controlled Fluctuators (65%) whose response persisted (FC_P in Fig. 1), while the remaining 35% were controlled Fluctuators with “wearing-off” (FC_{WO} in Fig. 1). As expected, Fluctuators were more likely to have early morning bradykinesia and a significant response to levodopa (Fig. 3c). Cases whose mDKS lay between 3-7 (i.e., in target) but with elevated PTD (in the shaded grey quadrant of Fig. 2c), presumably had high PTD because of fluctuations. UPDRS IV scores were two times higher when PTD≥20% ($p<0.001$ Mann Whitney). When UPDRS IV questions specific to dyskinesia (QIV.1 &IV.2) were examined, the median scores were “0” when PTD<20% and “2” for PTD≥20% ($p<0.001$ Mann Whitney).

PTB and Clinical Scales

The relationships between UPDRS III and Total scores and Fluctuator classifications were examined (Fig. 3d and 3e). Scores from both scales were highest in uncontrolled non-fluctuators (NFU), lowest in controlled non-fluctuators (NFC) and intermediate in fluctuators (F). Fluctuators whose LR response entered and remained in target (FC_P) had lower UPDRS III and total scores than other Fluctuator categories.

The clear trend for PTB to increase with increasing UPDRS III, UPDRS Total and PDQ39 scores is shown graphically (Fig. 4a, 4b and 4c) and by the correlations (Table 4). As described in the Methods (and in more detail in (24)), each 2 minut bradykinesia score was ascribed to one of 6 severity levels, with those being in Bradykinesia Severity Levels 3, 4 and 5 contributing to the PTB. Fig. 4d shows that when PTB is less than 60%, time in bradykinesia is spread evenly between high bradykinesia levels (Severity Level 5 corresponding to a UPDRS III≥60) and more moderate bradykinesia levels (Severity Levels 3 and 4). However, when PTB is above 60%, bradykinesia is predominantly in Severity Level 5. This is relevant because the clinical scales correlate better with percent time in Severity Level 5 than they do with PTB (Fig. 4a, 4b and 4c). PDQ39 Activities of Daily Living sub-score also correlated with PTB and percent time in Severity Level 5 (Table 4), whereas the motor sub-score was not significantly related (data not shown). In summary, there is a correlation with PTB and percent time in more severe bradykinesia and clinical scales and fluctuation categories with higher PTB are likely to have higher UPDRS scores.

Table 4 Correlation between Clinical Scales and PTB and Percent time in Level 5.

Clinical Scale	Severity Level	Pearson ρ	*p-value*	95% CI
UPDRS III	PTB	0.4	<0.0001	0.26 - 0.54
	Percent time in Level 5	0.42	<0.0001	0.28 - 0.55
UPDRS Total	PTB	0.34	<0.0001	0.18 - 0.48
	Percent time in Level 5	0.37	<0.0001	0.20 - 0.51
PDQ39	PTB	0.35	<0.0001	0.18 - 0.49
	Percent time in Level 5	0.37	<0.0001	0.21 - 0.51

Correlation between the PTB and clinical scales and between Percent time in levels of bradykinesia severity and clinical scales, shown graphically in Fig. 3a, b and c. The CI denotes Confidence Interval and p-value refers to significance level for Pearson's correlation.

Response to treatment

PKGs and UPDRS scores were available from before and after a change in oral therapy directed at improving bradykinesia in 57 subjects whose mBKS≥23 in the first PKG. The data is shown for the purpose of comparing changes in PTB with changes in other clinical scales (Table 5) and not to discuss the merits of treatment. Significant reductions in the UPDRS III and UPDRS Total were noted (Table 5), however the PTB fell by a greater percentage than either clinical scale. This proportional change would be greater if it had been referenced to the upper limit of the "normal" range (i.e., 30%) rather than 0%. If treatment is effective in reducing PTB, then a reduction in proportion of uncontrolled and increase in controlled fluctuators following treatment might be expected. The proportion of uncontrolled non-fluctuators decreased (38% to 25%) while the proportion of controlled non-fluctuators increased (18% to 27%, p=0.004 for Chi-square test). This change resulted from 14% of cases changing from uncontrolled non-fluctuators to fluctuator and 15% changing from Fluctuator to controlled non-fluctuators with 12% fluctuators changing to a fluctuator category with less PTB. There was no change in category in 51% of cases.

Table 5 Changes in Clinical and PKG measures following treatment for bradykinesia or dyskinesia

Table 5a			Mean (Std)	Δ%	*p* value
PwP treated for bradykinesia	Hohn &Yahr		2.4 (1)	n/a	n/a
bradykinesia score≥23	Years of PD		5.7 (3.8)	n/a	
N=57	PDQ39	before	29.8 (19.4)		
		after	25.6 (19.1)	14.1%	0.26
	UPDRS III	before	38 (10.2)		
		after	32.7 (10.9)	13.9%	0.008
	UPDRS Total	before	65.8 (18.4)		
		after	55.7 (20.5)	15.4%	0.003
	mBKS	before	29.4 (4.2)		
		after	27 (4.3)	8.2%	0.002
	PTB	before	63 (22)		
		after	50 (24)	20.6%	0.004
Table 5b					
PwP treated for dyskinesia	H&Y		2.4 (0.7)	n/a	n/a
PTD≥20%	Years of PD		9.4 (5.8)	n/a	n/a
N=27	UPDRS IV	before	7.7 (4)		
		after	4.3 (4.3)	44.2%	0.0009
	UPDRS Total	before	58 (18)		
		after	45 (23)	22.4%	0.010
	PTD	before	42 (20)		
		after	23 (16)	45.2%	0.0007
	mDKS	before	14 (13)		
		after	6.2 (4.3)	54.9%	0.0006

Mean and standard deviation (in parenthesis) of each measure before and after the therapeutic intervention. Δ% is the percentage change of the score following treatment. The p-values were obtained from Welch's t-test where the null hypothesis is that the mean of before and after are the same and the alternative hypothesis is that the means are not the same.

The demographics and clinical scales (Table 5) of 27 PwP whose PTD was greater than 20% were treated explicitly to reduce dyskinesia (13 with deep brain stimulation). These cases had a longer disease

duration than cases whose PTD<20% (9.4 v 6.3, p=0003) and higher Levodopa Equivalent Daily Dose than cases whose PTD<20% (1037 v 687, p=0.0004). There were improvements in clinical scores ranging from 27% (for UPDRS Total) to 75% for UPDRS IV and the point of showing this data is that the changes in PTB were of similar sensitivity. As noted above this proportional change would be greater if it had been referenced to the upper limit of the normal range (20%) and not 0%.

Discussion

The aim of this study was to present the objective measurement of the percentage of time that bradykinesia or dyskinesia scores are above a target (PTB and PTD) as a means for assessing levels of treatment and fluctuations in PD. While PTB and PTD bear superficial similarities to diary recordings of “on” and “off”, they differ in measuring *signs* of altered dopamine transmission rather than *symptoms* of altered dopamine transmission and in the use of an objective measurement against a target range. Nevertheless, the approach used here in developing PTB and PTD does incorporate the fundamental issue of a target range, representing adequate treatment of bradykinesia and dyskinesia. This issue must be addressed by any system of objective measurement of fluctuations developed in the future.

The target for bradykinesia was chosen to reflect the boundary between control subjects and PwP: thus, PwP whose bradykinesia scores are in target for >70% of the time (PTB<30%) have similar scores to controls. Indeed, most PwP with low PTB (Fig. 3) were controlled non-fluctuators with little or no measurable levodopa response or early morning bradykinesia and typical of early PD. The remaining cases whose scores fell in the shaded quadrant of Fig. 2b did have a response to levodopa that was sufficient to lower bradykinesia levels into the controlled range but “wore-off” prior to the next dose and consequently, added to PTB. In these cases, it is plausible that reducing the levodopa dosing interval will remove “wearing-off” and reduce PTB. Cases whose scores lie in the shaded area quadrant of Fig. 2b are controlled when measured by the median bradykinesia score (mBKS) but not when measured by PTB. While future studies are required to demonstrate which of these two (mBKS or PTB) provides better targets for assessing control of PD, at this point, maintaining PTB in the control range seems likely to be the more sensitive measure of whether fluctuations have been controlled. In this context, it is relevant that PTB seemed to be more sensitive measure than mBKS when measuring the treatment of bradykinesia (Table 5a). When PTB is high (≥75%), most cases are Non-Fluctuators with high levels of bradykinesia (including early morning bradykinesia) and without an LR. There may be many reasons for a lack of LR, including undertreatment and this can be tested by increasing dopaminergic stimulation: 14% of cases responding to treatment of bradykinesia (Table 5a) were non fluctuators converting to fluctuators.

In many conditions where measurement is routine, targets are based on physiological upper limits or on clinical outcomes which may include health economic arguments. These targets are not immutable and often become more stringent with more evidence and better therapies: targets for lipids and blood pressure are examples. The target for mBKS and mDKS were referenced to physiological upper limits and supported by expert opinion (21). However, an important validation of a target is when it is used to guide therapy to bring the parameter in question into the “control” range, with consequent improvement in

outcomes. A recent study reported improved outcomes when using PKG parameters and targets to guide treatment (16). In that study, the mean UPDRS III of participants whose PKG parameters were in target was 27.4 (±7.9), noting that 35.3 (mean plus 1 standard deviation) is comparable to the UPDRS III target used in this study (35: see Table 3). A search of the literature provided little insight as to what might be a suitable target in terms of UPDRS III scores, but this would suggest that the current threshold is reasonable even though future studies might argue for modification. The PTB and the PTD are (respectively) closely linked to mBKS and mDKS in their derivation and their targets are all based on normative data. It is therefore to be expected the levels of 30% for PTB and 20% for PTD would also triangulate with mBKS and mDKS thresholds (Fig. 2). However, PTB≥30% does not translate easily into "hours off", which is the terminology from diaries that is more familiar to the clinician. Percent of available time between 09:00-18:00, rather than absolute "time above target", is used because subjects can be asleep, inactive, exercising or not wearing the PKG for varying times each day. PTB≥30% can be converted to nominal hours above target between 09:00 and 18:00 (Fig. 5) and a PTB=53% is nominally equivalent to spending 3 of the 9 available hours above target. As 2-3 hours "off" time that cannot be rectified by manipulation of oral therapy is taken as an indication for device assisted therapy (30), this would suggest that a PTB~50% might carry the same implications. This also suggests that when measuring percent improvement after treatment it should be referenced to PTB=30% and not 0%: the PTB of PwP treated for bradykinesia in Table 4 improved by 21.6% (63% to 50%) when referenced to 0%, but would improve by 39% (33% to 20%) when referenced to 30%.

The differences between history derived measures for "off time" or "time in dyskinesia" and those derived using PTB and PTD here, mean that the former cannot be used as a gold standard to assess the performance of objective measures. Diaries and the PKG were compared (18) using a similar measure of PTB and PTD and showed a modest correlation with hours "off" and "on" using diaries and there is only modest concordance between diaries and video recordings (6, 31). At a practical level, diary data was not part of the studies from which the data was obtained. The construct validity of the PTB and PTD is best found by examining the relationship between PTB and PTD with clinical scales and their behaviour in relation to clinical interventions. There was also a well correlated increase in PTB in association with an increase in UPDRS III, UPDRS Total and PDQ39 (Fig. 4). Furthermore, both PTB and PTD decreased following treatments directed at reducing bradykinesia and dyskinesia, respectively. These treatments were chosen because they resulted in significant changes in the scores from clinical scales and the relevant point is that changes in PTB and PTD were at least commensurate, if not larger. Taken together, the relationship with clinical scales and the changes following treatment are *prima facia* evidence of validity of these two scores. A further validation is that the severity of PTB associated with the different types of fluctuators (Fig. 3) was what might be expected clinically.

The reported incidence of fluctuators and "wearing-off" in PD depends, in part, on the population being studied. The cohort of PwP in this study were drawn from a mixture of specialist and non-specialist clinics who filled the specific criteria of the study to which they were recruited (15, 16). As a result, late-stage PD is relatively underrepresented (Table 1). In this study, only the period of 165-210 mins after the first dose was assessed for "wearing-off" and only following the first dose. As "wearing-off" can occur at

doses later in the day and may take longer than 3 hours after a dose to appear, the proportion of PwP with “wearing-off” may be underestimated. However, fluctuators were defined by the presence of substantial LR, which is almost always associated with a short duration of benefit to levodopa and is a reasonable estimate of the proportion with a propensity to “wear off”.

Artefacts can affect the PKG results. Detection of bradykinesia at the time of the first dose will depend on requirements similar to a levodopa challenge test: the subject should be out of bed and active, having not consumed prior medications for a minimum of 8 hours. The analyses described here relate only to the response to the first dose of the day and will overlook “wearing-off” with levodopa response lasting more than 3½ hours. Future studies could examine the response to subsequent dose, provide longer time for “wearing-off” to occur and look in greater detail at variability in the duration to time to response. The initial description of the PKG as a model of the levodopa challenge test (24) noted that this is best studied on later doses when inactivity is less likely.

While this study used the PKG, the methods and concepts are relevant to any continuous objective measure. Since increased bradykinesia, as measured by the UPDRS III, is associated with worse outcomes and quality of life, it is surprising that more attention is not given to objectively reducing bradykinesia. Studies aimed at treating bradykinesia with the aim of recuing it until it reached an objectively measured target have led to improved clinical scores (15, 16). The motor component of disability (mostly as a consequence of bradykinesia) contributes directly to poor quality of life (32-34), implying that improving motor symptoms would improve quality of life. Motor fluctuations and dyskinesia also affect quality of life (34-38) (and see discussion in Dodel et. al. p1022 (35)) and the presence and management of fluctuations have a significant influence on quality of life (38-41). Although diaries ask PwP to distinguish “troublesome” dyskinesia from other forms of dyskinesia, this is problematic because of the impaired self-awareness of dyskinesia discussed earlier. However, objective measurement of dyskinesia permits dyskinesia with larger excursions or greater energy to be quantified separately from less severe dyskinesia. Future studies might establish whether these factors impact more severely on quality of life.

Conclusions

Management of PD in the clinic and assessment of outcomes clinical trials of therapeutic agents for PD depends heavily on accurate assessments of the severity of fluctuations and dyskinesia. The only means for assessing the severity of fluctuations and dyskinesia has been the subjective assessment of the PwP whereas an objective measurement has long been lacking. This study addresses the requirement of a target range when objectively measuring fluctuations and dyskinesia and provides measures of the proportion of a PwP’s day that bradykinesia (PTB) and dyskinesia (PTD) are above target as useful measures of fluctuations and dyskinesia. Treatments directed at treating bradykinesia, fluctuations and dyskinesia in this study and reported elsewhere (16) result in improvements in PTB and PTD. Thus, the measures of fluctuation and time in dyskinesia described here have the potential to improve

management in routine clinical care and measurement in clinical trials. Accurately measuring fluctuations, PTB, and PTD is arguably a key step towards improving quality of life in PD.

Abbreviations

EMB Early Morning Bradykinesia all defined in figs

F Fluctuators

FC_P Fluctuator Controlled Persisting

FC_{WO} Fluctuator Controlled wearing-off

FU_P Fluctuator Uncontrolled Persisting

FU_{WO} Fluctuator Uncontrolled wearing-off

LEDD Levodopa Equivalent Daily Dose

LR) Levodopa Response

mBKS median Bradykinesia Score

mDKS median Dyskinesia Score

NFC Non Fluctuator - Controlled

NFU Non Fluctuator - Uncontrolled

PD Parkinsons Disease

PTB Percent time bradykinesia

PTD Percent time Dyskinesia

PKG Parkinson's KinetiGraph

PwP People with Parkinsons Disease

UPDRS Unified Parkinsons Disease Rating Scale

Declarations

Ethics approval and consent to participate

This is a study of a database collected in previous studies and approved by St Vincent's Hospital Melbourne Human Research and Ethics Committee. All studies were carried out in accordance with the guidelines issued by the *National Health and Medical Research Council of Australia* for Ethical Conduct in Human Research (2007, and updated May 2015) and in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Clinical characteristics of participating subjects and inclusion criteria into the analyses are discussed below.

Consent for publication

Not applicable

Availability of data and materials

Not applicable.

Competing interests

Global Kinetics (GK) is the manufacturer and distributor of the Parkinson's KinetiGraph. HK and NS are employed by GK. MH has financial interests in GK. GK management had no direct role in the instigation, design collection, analyses, or interpretation of data, in the writing of the manuscript, nor have they been consulted as to whether the data should be published.

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Author contributions

HK and NS have developed the analytical variables used in this paper. MH has collected the clinical data. The manuscript was written and prepared by MH with editing and discussions from HK and NS.

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Authors' information (optional)

Not applicable.

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Figures

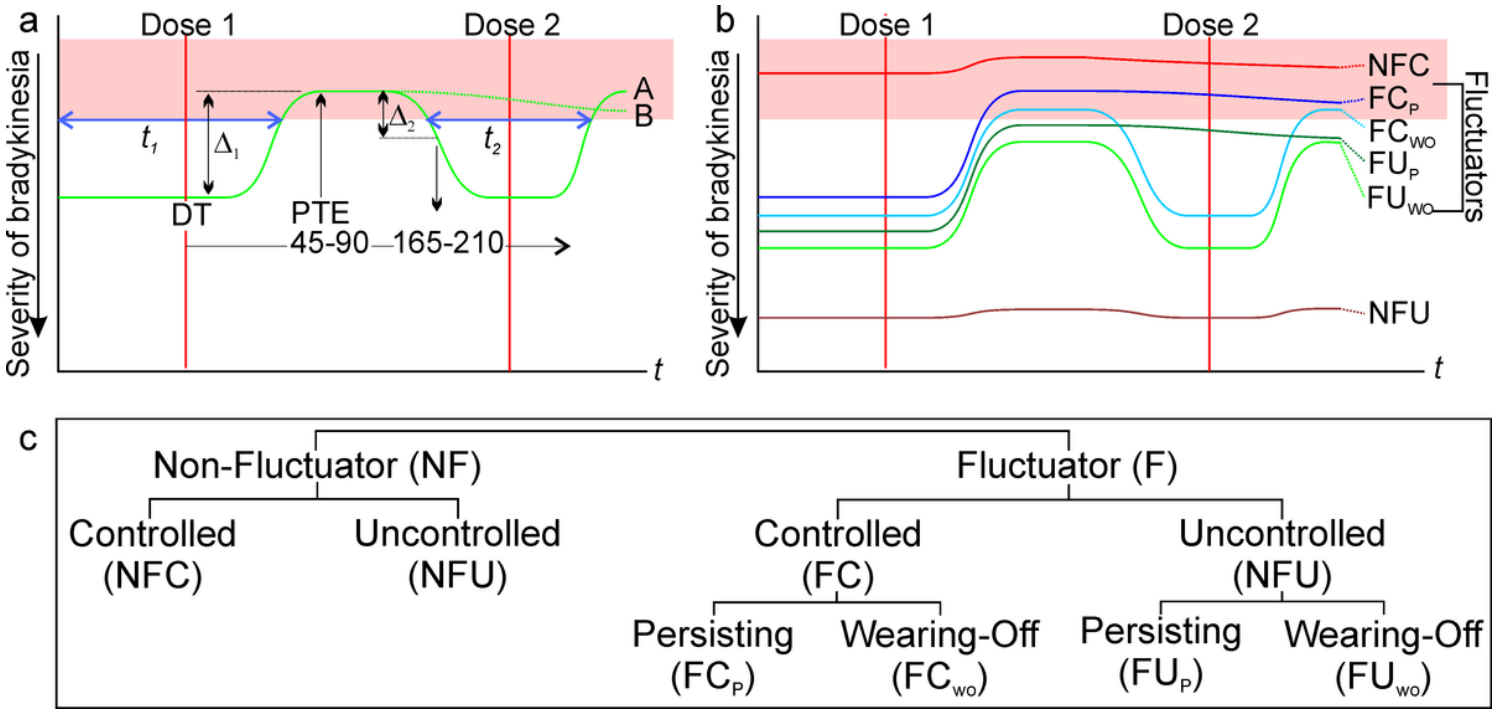

Figure 1

The Levodopa Response and Categorization of Fluctuators In panels 1a and 1b, the X axis shows time (t) of day between the first and second dose (red vertical lines) and the Y axis shows bradykinesia increasing in severity toward the bottom of the graph. The target range for bradykinesia is shown by orange shading. a. depicts a case where the severity of early morning bradykinesia at the time of the first dose (DT) is above the target range. The LR is the difference in bradykinesia severity (Δ1) at time of peak levodopa effect (PLE: 46-90 minutes after the first dose) and at DT. Two examples of subsequent clinical response to the first dose are shown. The full green line (A) shows a case with “wearing-off” which occurred when the Severity Level increased by “1” (Δ2) between 165 and 210 minutes after first dose time (depending on time of peak levodopa effect latency). The green dotted line (B) shows a persisting response without significant decline from the best LR response. Blue lines (t1 and t2) immediately under the target range indicate when Line “A” is above target and conceptually, PTB is the time represented by this line (t1 + t2) as a percentage of total time (t). b. represents 6 fluctuator categories (defined at the right of each curve) that are described in the Methods. c. is a flow diagram of the fluctuator classification and the naming convention.

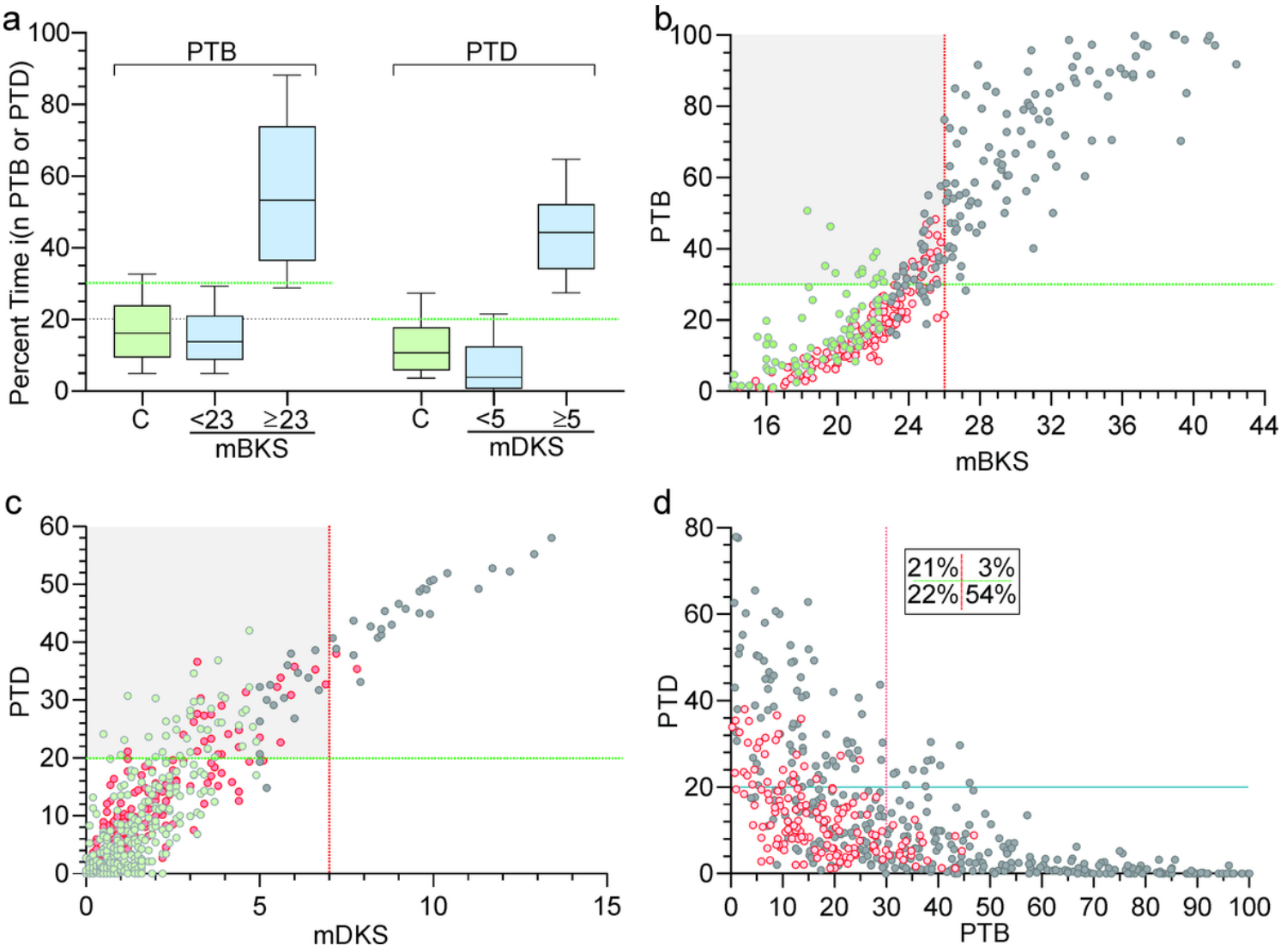

Figure 2

Please see the manuscript file for the full caption

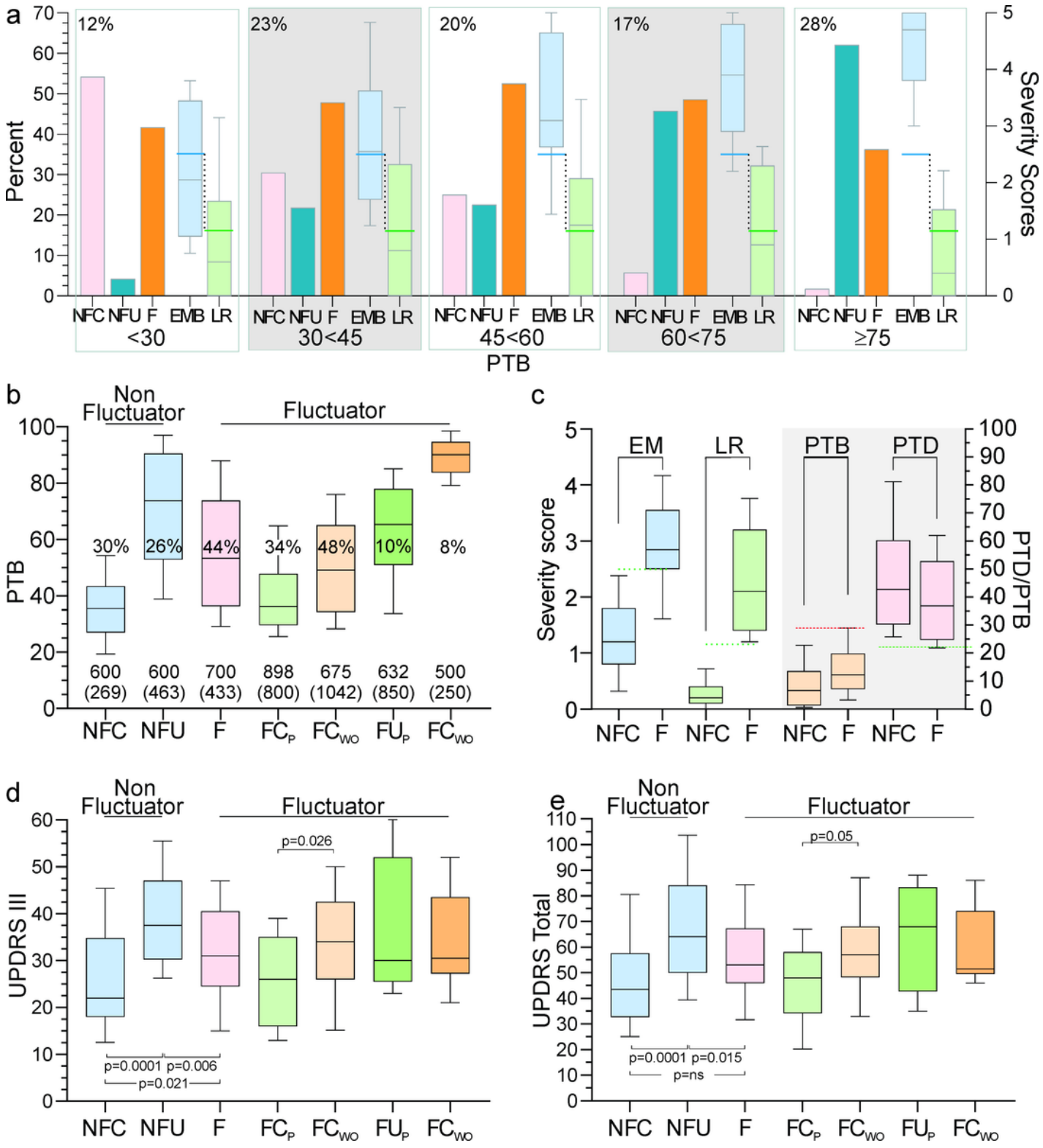

Figure 3

Please see the manuscript file for the full caption

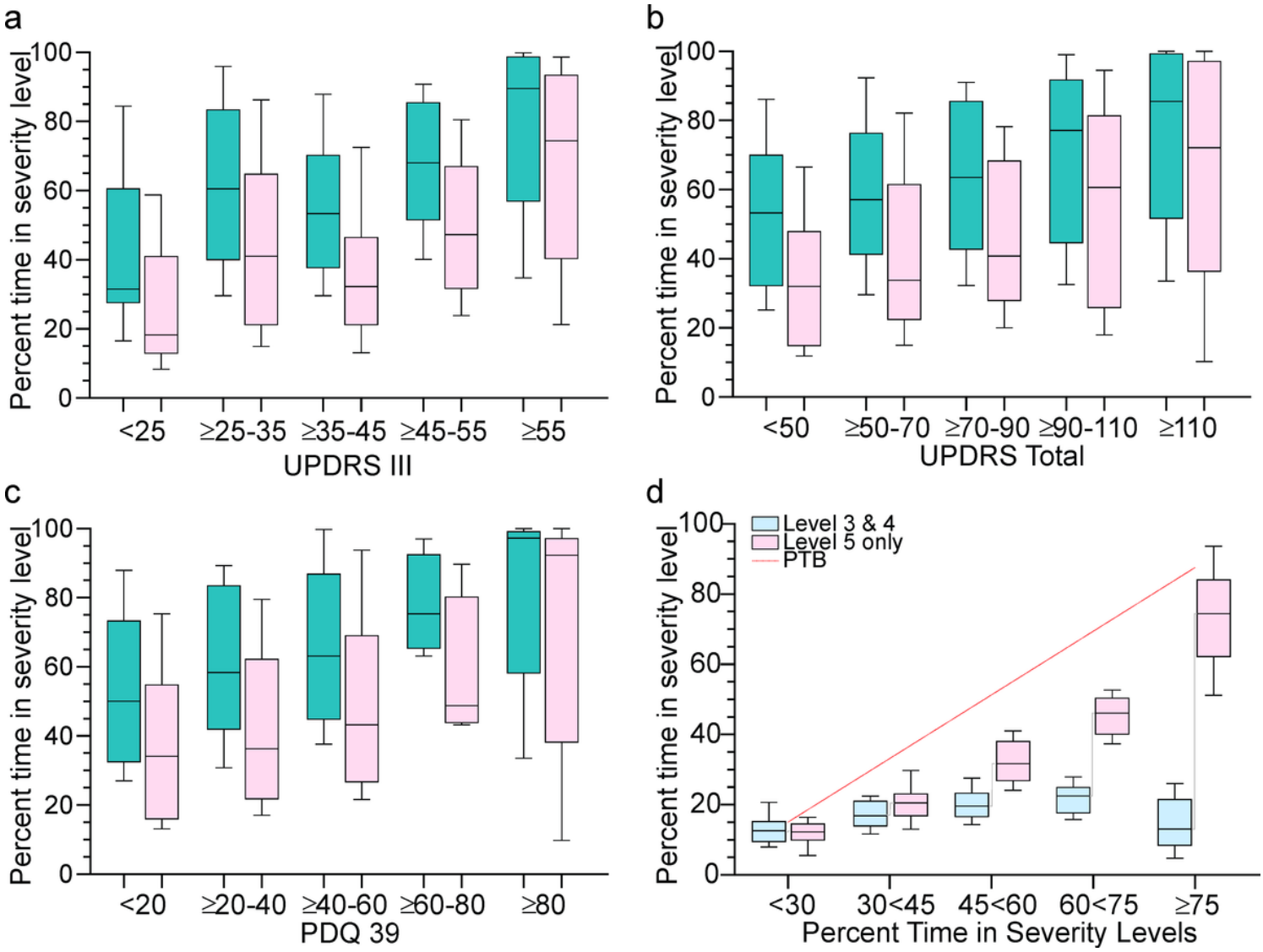

Figure 4

Please see the manuscript file for the full caption

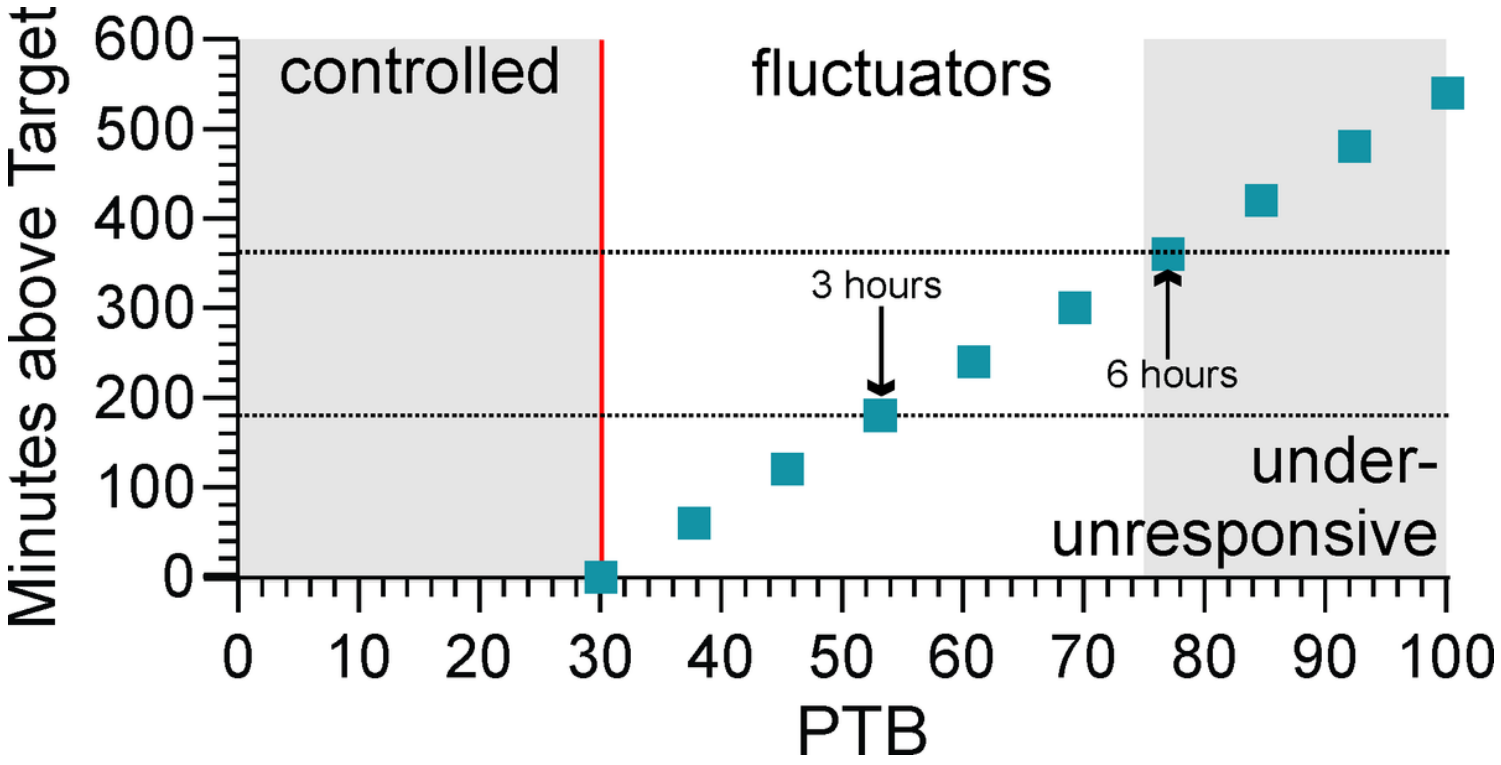

Figure 5

PTB and relationship to hours in bradykinesia The percent time in bradykinesia (PTB: X axis) is converted to minutes above target (Y axis) considering 9 hours per day (from 9am to 6pm) for PTB≥30% (assuming PTB<30% is in the control range and equal to zero) using the formula: minutes= (PTB-30) * 7.714.