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Research article

Antiparkinsonian medication masks motor signal progression in de novo patients☆

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ABSTRACT

Patients not yet receiving medication provide insight to drug-naïve early physiology of Parkinson's Disease (PD). Wearable sensors can measure changes in motor features before and after introduction of antiparkinsonian medication. We aimed to identify features of upper limb bradykinesia, postural stability, and gait that measurably progress in de novo PD patients prior to the start of medication, and determine whether these features remain sensitive to progression in the period after commencement of antiparkinsonian medication.

Upper limb motion was measured using an inertial sensor worn on a finger, while postural stability and gait were recorded using an array of six wearable sensors. Patients were tested over nine visits at three monthly intervals. The timepoint of start of medication was noted.

Three upper limb bradykinetic features (finger tapping speed, pronation supination speed, and pronation supination amplitude) and three gait features (gait speed, arm range of motion, duration of stance phase) were found to progress in unmedicated early-stage PD patients. In all features, progression was masked after the start of medication.

Commencing antiparkinsonian medication is known to lead to masking of progression signals in clinical measures in de novo PD patients. In this study, we show that this effect is also observed with digital measures of bradykinetic and gait motor features.

1. Introduction

Newly diagnosed, unmedicated (often referred to as "de novo") Parkinson's Disease (PD) patients allow the analysis of the purest state of PD in the hope of developing new prognostic and disease monitoring markers, without the overlaid effect of dopaminergic medication. However, the early use of levodopa is advocated in current clinical guidelines [1,2], which means that pharmacologically unaffected PD is only briefly observed.

There are only a few studies that focus on the measuring of motor symptoms in the de novo PD population (for an up-to-date review

☆ None.

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of literature see Table 1). Some of these investigate cross-sectional differences between PD and healthy participants or examine progression in the unmedicated state only. Two studies, by Marras et al. and van den Heuvel et al., studied large cohorts over many visits after the start of medication, using clinical rating scales such as the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [3,4]. These rating scales are the current gold standard in clinical practice, but they may be insensitive to small changes in movement in early-stage patients, and can also be affected by inter-rater variability [5–7]. Wearable movement sensors and digital forms of assessment are becoming increasingly popular in the study of neurodegenerative diseases [7–13] because of their precision and objectivity, and have been shown to discriminate between healthy adults and PD patients of different disease severity [11,14]. Three studies have used wearable devices in de novo patients as they are started on medication, but they have only examined two or three timepoints. Thus although the use of wearable inertial sensors can identify medication-induced improvements of motor features in de novo PD [15–17], less is known about the effect of levodopa on the longitudinal progression of measurements made using such systems.

The aim of the present study was to identify kinematic features that progress with time in drug-naïve patients and explore how the start of medication affects this progression. In this study, we captured standard clinical rating scales and kinematic features using wearable devices. Individuals with de novo PD were assessed every 3 months, over a period of 2 years, during which they started receiving medication at a natural time determined in the usual way by them and their physician. Three different movement tasks were utilised, namely, walking, postural balance, and upper limb bradykinesia testing. Bradykinesia components measure a variety of higher complex and primitive motor execution levels, which have all been correlated with overall disease progression and treatment efficacy [18,19]. The tasks require adequate movement planning and sensory integration, leading to sequential execution of repetitive movements both in small (finger-tapping) and larger (pronation supination) muscle groups [20]. Features of gait are classically known to be affected in the progression of PD [21], with impairments in the speed of walking, step length [22] amplitude of arm swing [23], and postural control [17] becoming evident over the course of the disease. Our hypothesis was that progression signals observed in the unmedicated state would be attenuated or even masked once symptomatic medication was started.

Table 1
Review of current literature on study of motor symptoms in de novo Parkinson's Disease.

Study	N	Follow-up	Technology	Features	Conclusions
Cross-sectional data					
Ricci et al., 2020 [14]	30 de novo PD/ 30 HC	N/A	wearable sensors	pronation-supination, leg agility, pull test, toe tapping, TUG	HC vs PD discrimination (85–95% accuracy, 92–95% AUC).
Mancini et al., 2011 [32]	13 de novo PD/ 12 HC	N/A	postural sway	jerk of lower trunk, root mean square and the frequency dispersion of postural sway	Accelerometer features can distinguish PD from HC
Longitudinal – tracking progression, not designed to measure effects of medication					
Skidmore et al., 2022 [33]	301 de-novo PD/127 HC	every 6 months for 5 years	UPDRS + other clinical scales	Hoehn and Yahr stage, UPDRS features	Faster progression for PIGD
Salarian et al., 2007 [34]	12 de novo PD/ 14 HC	every 6 months, for 1.5 years	wearable sensors	Turns	PD vs HC: Increased turning durations and last step (before turn) delay. Turning duration as progression marker.
Schüpbach et al., 2010 [35]	12 de novo PD	Every 6 months for 1 year	UPDRS + other clinical scales	Motor part UPDRS features	Progression in rigidity and postural tremor but not bradykinesia.
Longitudinal – measure effects of medication – prescribed start of therapy					
Kwon et al., 2017 [36]	24 de novo PD/ 27 HC	Tested before and 1 h after starting medication	Walking mat	Spatio-temporal gait variables, gait variability and asymmetry	Stride length, walking speed, and cadence increased, and stride time decreased with medication.
Ricci et al. [16],	36 de novo PD	6 and 12 months after start of medication	Wearable sensors	Bradykinesia, pull test, timed up and go, tremor	L-dopa improved features of all but tremor task
Di Lazzaro et al., 2021 [15]	40 de novo PD	6 and 12 months after start of medication	Wearable sensors	Bradykinesia, timed-up-and-go, pull test, tremor (upper limbs)	All motor tasks had at least one feature (except tremor) that improved with levodopa
Marras et al., 2011 [4]	1606 de novo PD (combined)	Every 3 months for 2 years	UPDRS + other clinical scales	Baseline UPDRS, employment, education, age, tremor, MMSE, smoking, asymmetry score, site of onset	Higher UPDRS, full time employment, lesser smoking history, onset on the left all associated with initiating levodopa therapy faster
Longitudinal – measure effects of medication – natural start of therapy					
Mancini et al., 17–38 2012 [17]	13 de novo PD/ 12 HC	After 3, 6 and 12 months	Wearable sensors	2-min postural balance test	Slight decrease in sway dispersion and velocity compared to an increase in untreated
Van den Heuvel et al., 2021 [3]	432 de novo PD	Every 6 months, for 4 years	UPDRS + other clinical scales	Observed the natural introduction of meds across two-year period in patients, compared earlier vs. later meds	No difference between early-vs delayed medication onset. Slight improvement by year 2 if treated at an earlier stage

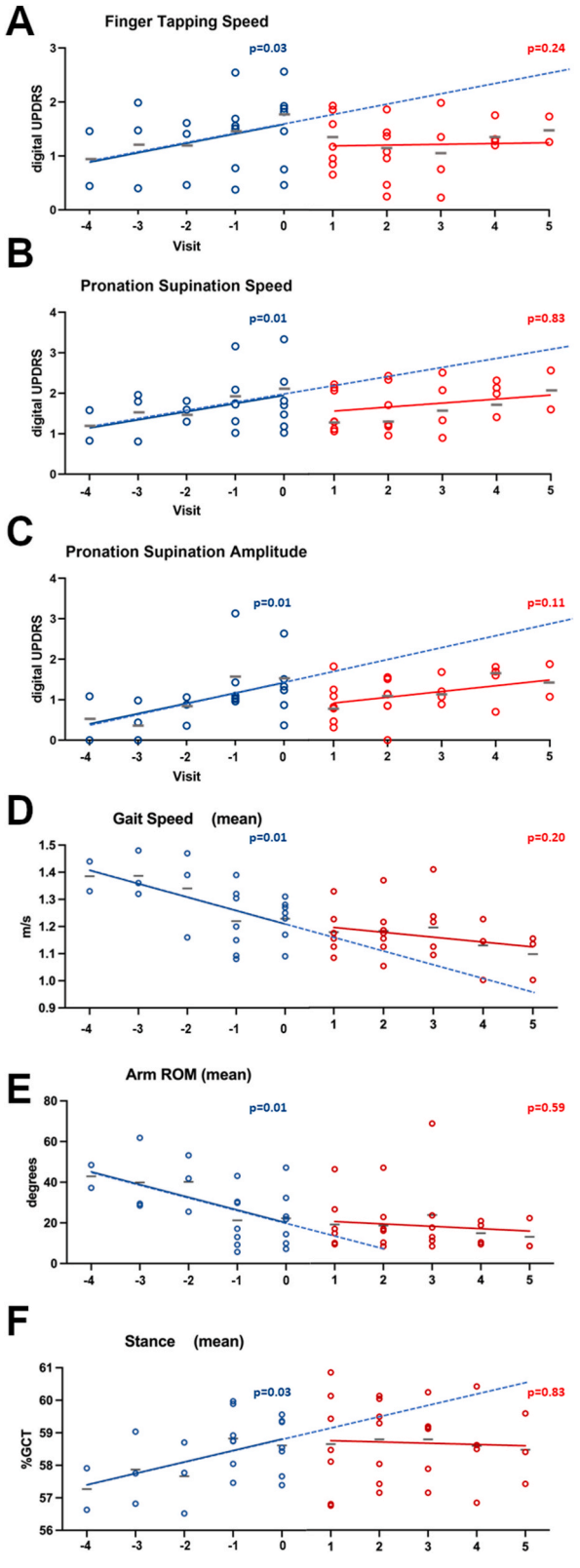

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Fig. 1. Progression of finger tapping speed (A), pronation supination speed (B), pronation supination amplitude (C), gait speed (D), arm ROM (E) and the duration of stance phase (F) over time, before and after introducing medication. Visits are at three-monthly intervals. The significance levels are presented for the linear regression line of best fit. Dotted line shows an extrapolation of the pre-medication condition, added to illustrate the graphical differences in the post-medication condition. MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale, ROM = Range of Motion, %GCT = percentage of Gait Cycle Time.

2. Results

Three digital bradykinetic and three digital gait features were found to significantly (linear regression $p < 0.05$) progress with time prior to onset of medication. These were: finger tapping speed, pronation supination speed, pronation supination amplitude, arm range of motion (ROM), duration of stance phase as a percentage of gait cycle time, and gait speed.

Following commencement of antiparkinsonian medication, there was an improvement in each measure (i.e. acute shift towards normal values) followed by a flattening of the curve indicating that further progression was masked (Fig. 1).

None of the standard clinical scores, including total MDS-UPDRS, MDS-UPDRS part II (motor aspects of daily living), MDS-UPDRS part III (motor examination), and the PDQ-39 quality of life measure, showed significant progression over the period studied, either before or after the onset of pharmacotherapy (Fig. 2).

A retrospective study of all clinical notes, patient communication and recorded material was conducted to look for feedback relating to the potential for excessive burden relating to the use of wearable devices on participants. One case of device malfunctioning was recorded across the entire dataset. This was quickly rectified, and the participant was happy to repeat the task. All remaining recorded feedback was positive or neutral, albeit this was not formally collected as part of the study protocol. All but two participants completed all nine visits of the study. In a review of reasons for discontinuation, the burden of technology was not noted (one participant was discontinued due to the COVID-19 pandemic, and one withdrew due to family difficulties, unrelated to the study).

3. Discussion

In this study we have examined three key aspects of PD, postural stability, gait disturbance, and bradykinesia, quantifying each in detail with wearable sensors. This permitted the identification of six features displaying progression over time in early stage unmedicated patients. On commencement of medication, there was a clear change in the behaviour of these features – in every case there was a shift towards normal values followed by masking of discernible progression over time.

The masking of progression signals by symptomatic medication is a major problem for clinical trials, particularly of potentially Disease Modifying Drugs (DMD). Such trials rely on being able to accurately track disease progression, so that a beneficial effect can be observed as a reduction in the progression rate [24]. The need to track progression accurately has driven the widespread investigation and adoption of wearable technology, and such technology clearly does have advantages in terms of sensitivity to change, as exemplified by the fact that several variables from the wearable devices in this study show progression in the unmedicated state, while the standard measures do not. The key point here however is that the signal from the wearable measurements disappears on starting medication. In other words, the greater sensitivity to change in wearable data compared to standard measures does not make wearable data immune to the well-known difficulties in tracking progression in the presence of symptomatic treatment.

There are some possible ways to tackle this problem. Some DMD trials could be limited to de novo participants. Arguably these are the people with most to gain from these agents. However, de novo patients are a small minority of PD patients so recruitment may be challenging, and generalisability of trial results to the majority of PD patients would be unclear. Another option would be to stop antiparkinsonian medication for study assessments. However, although levodopa is a symptomatic treatment (it has no disease-modifying effect [25]), it does have some enduring effects: histopathological, molecular and clinical studies in animal models and humans alike point to wide-ranging effects on brain structure and signalling [26–29]. Thus, the start of pharmacotherapy is a unique, once in a lifetime physiological phenomenon, and subsequent withholding of medication for assessment may not replicate the parkinsonian state that would have been present if the patient had never been medicated. In addition, the withholding of antiparkinsonian medication may be a stressful experience that itself can affect the severity of parkinsonian symptoms. A third possibility is the use of non-somatomotor markers, which may be less affected by symptomatic antiparkinsonian medication. A promising candidate here is the measurement of saccadic eye movements [12,30].

It is important to ensure that the benefits of digital technology in terms of added granularity of measurements can be achieved without excessively burdening patients, compared to standard clinical measures. The digital measurements in this study were obtained during standard clinical examination. The MDS-UPDRS, sway task and 2-min walk are normally used in a movement disorder clinic [31]. The application and removal of these sensors takes less than 1 min – they are similar to wearing fitness devices with an elastic Velcro strap. There were no technology-related dropouts from the study and none of the feedback from participants (actively solicited at the end of the study) mentioned that the addition of wearable sensors to their assessment constituted a significant burden.

The results of the current study need to be interpreted with some caution. Some of the features we identified (pronation supination speed and amplitude) do show a non-significant trend after the commencement of medication. This could be as a result of the limited sample number included in this study, and it is possible that with a larger sample size significant progression would have been seen at group level, thus making these features useful for disease progression tracking for medicated PD patients. We may also have not detected progression in some features in the unmedicated state, either due to the small sample size, non-pharmacological treatments or because they only progress later in the natural history of PD.

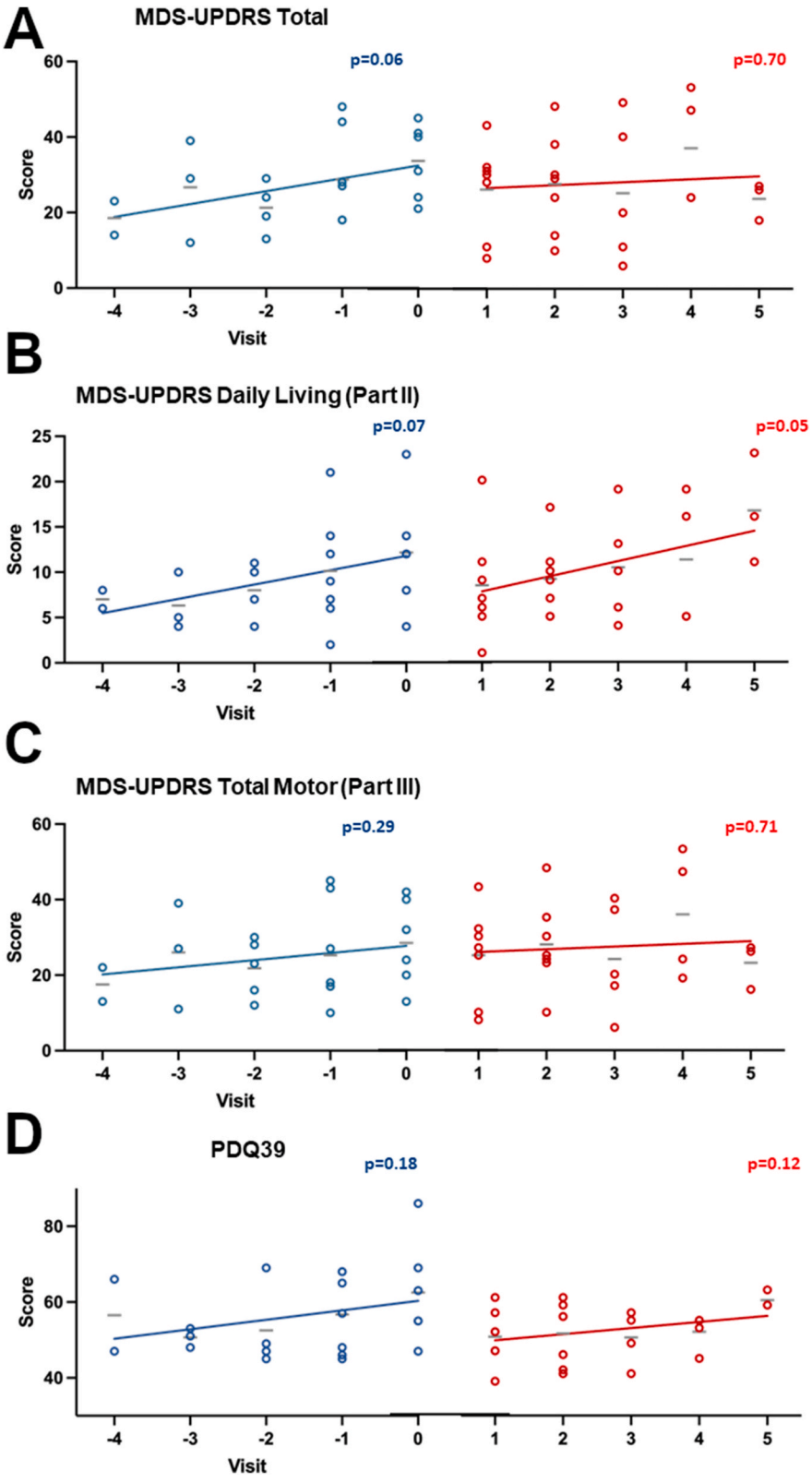

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Fig. 2. Progression of total MDS-UPDRS (A), MDS-UPDRS Motor Aspects of Experiences of Daily Living (Part II) (B), Motor MDS-UPDRS (Part III) (C) and PDQ 39 (D) scores, before and after introducing medication. Visits are at three-monthly intervals. The significance levels are presented for the linear regression line of best fit. MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale, PDQ 39 = Parkinson's Disease Questionnaire 39.

Nevertheless, the pattern in our results is clear: there is progression in multiple digitally-measured movement-related biomarkers in de novo PD patients, but this is obscured following the commencement of symptomatic medication.

4. Methods

The data were derived from the OxQUIP (Oxford QUantification In Parkinsonism) study conducted at the John Radcliffe Hospital in Oxford, UK (Research Ethics Committee approval 16/SW/0262). Informed consent was obtained. This longitudinal study recruited 18 patients with a diagnosis of idiopathic, unmedicated (de novo) PD. To be eligible for inclusion in the primary analysis, participants needed to complete at least 2 visits before and 2 visits after starting their antiparkinsonian medication (Table 2).

The participants were tested every three months across up to nine visits using the same battery of motor tests. The clinic dates were set individually from the date of recruitment. First, upper limb bradykinesia was measured using a single inertial sensor (Kinesia™ One, Great Lakes Neurotechnologies, Inc., Cleveland, OH) to capture the motion of the index finger. Kinematic data were collected during MDS-UPDRS finger tapping, hand movement, and pronation supination tasks. Second, gait analysis was performed using six Inertial Measurement Unit (IMU) sensors (Opal™, APDM, Portland, Oregon, USA). IMUs were worn by the participants on the sternum, lumbar region, and left and right wrists/feet during a 2-min straight level surface walk and a sway task with eyes closed for 30 s. Both sensors collected data at a sampling frequency of 128Hz. These devices were wirelessly connected to the APDM MobilityLab System (MobilityLab™, APDM) for the extraction of standard, manufacturer-specified motor features related to the walk and sway tasks (Fig. 3).

The wearable sensors measured a large number of variables (>160 features). In order to reduce the dimensionality of the dataset, we performed some initial feature selection as follows (Fig. 4). First, where the feature possessed left/right components we only analyzed features derived from the participant's most affected side.

For each participant we defined visit 0 as the last study visit before commencement of medication; visits going back in time prior to this were labelled −1, −2 etc. Visit 1 was the first visit after commencement of medication and subsequent visits were labelled 2, 3 etc. This allowed the time of onset of medication for all subjects to be aligned. We then analyzed the movement features over the period prior to medication (i.e. up to and including visit 0), looking specifically for a significant progression in the feature value over time. This analysis was not corrected for multiple comparisons because our priority was to avoid type 2 error and identify all features with possible progression in the unmedicated state. For those features where a significant change over time was observed, we repeated the regression analysis for the period after onset of medication (i.e. visit 1 onwards). Antiparkinsonian medication started before visit 1 is listed in Table 3.

Conflict of interest/financial disclosures

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Authors contributions

Maksymilian A. Brzezicki: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Niall Conway, Charalampos Sotirakis: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the

Table 2
Demographic information of all participants in the study and those eligible for primary analysis (completion of at least 2 visits before and 2 visits after starting the medication).

Group	Total	Eligible for inclusion
N	18	7
Mean age (range)	65 (57–75)	64 (58–68)
Gender (M:F)	8:10	2:5
Mean baseline MDS-UPDRS Motor Score (range)	25.5 (11–55)	25.4 (18–29)
Mean Hoehn & Yahr disease severity (range)	1.5 (1–2)	1.3 (1–2)
Mean Schwab & England activities of daily living scale (range)	96.7 (90–100)	97.1 (90–100)

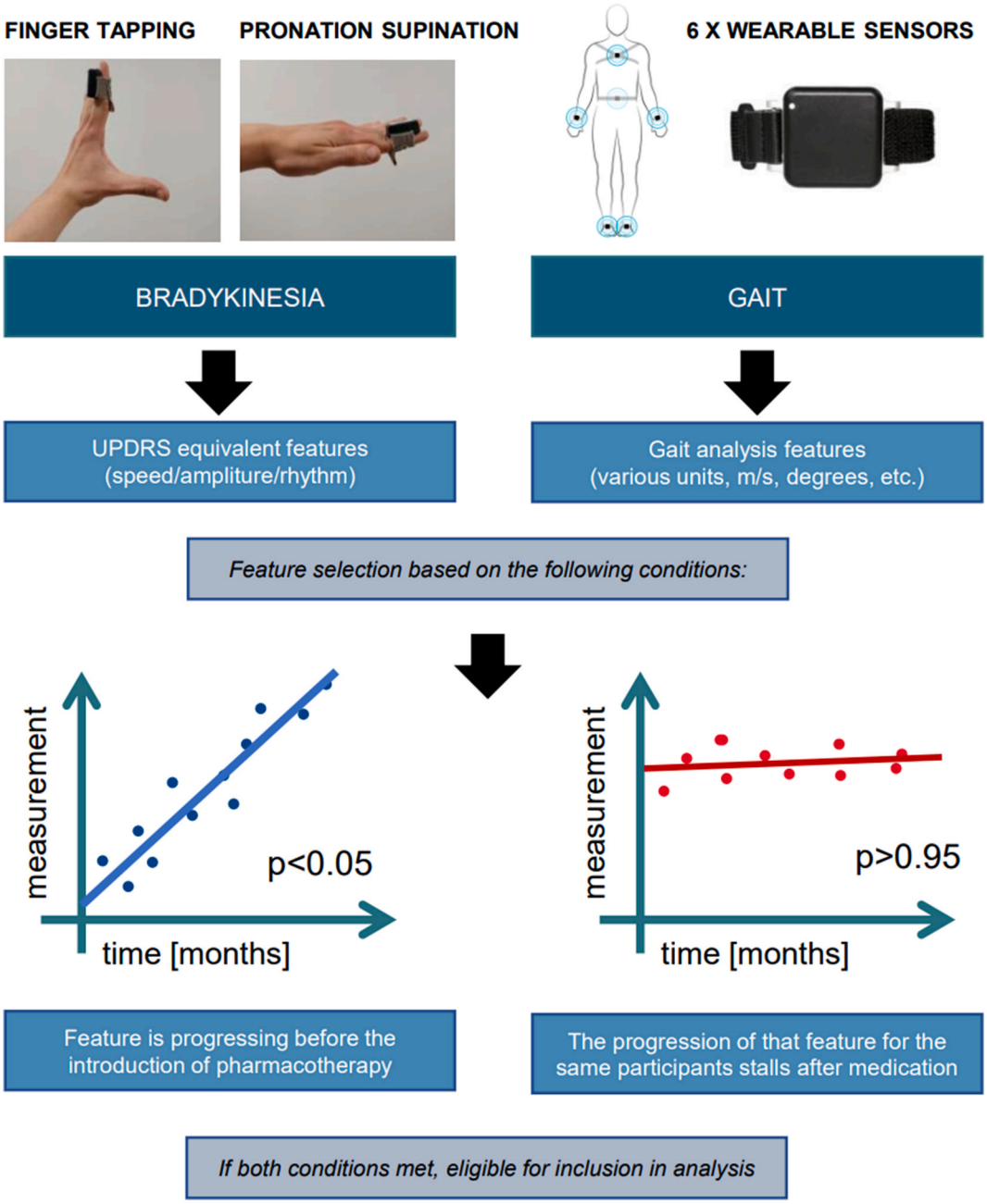

Fig. 3. Processing and selection of features included in the analysis. The measurements were obtained by applying wearable accelerometer and gyroscope sensors in two different tasks: gait (2 min walk) and bradykinesia subset of UPDRS.

paper.

James J. FitzGerald: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Chrystalina A. Antoniades: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data will be made available on request.

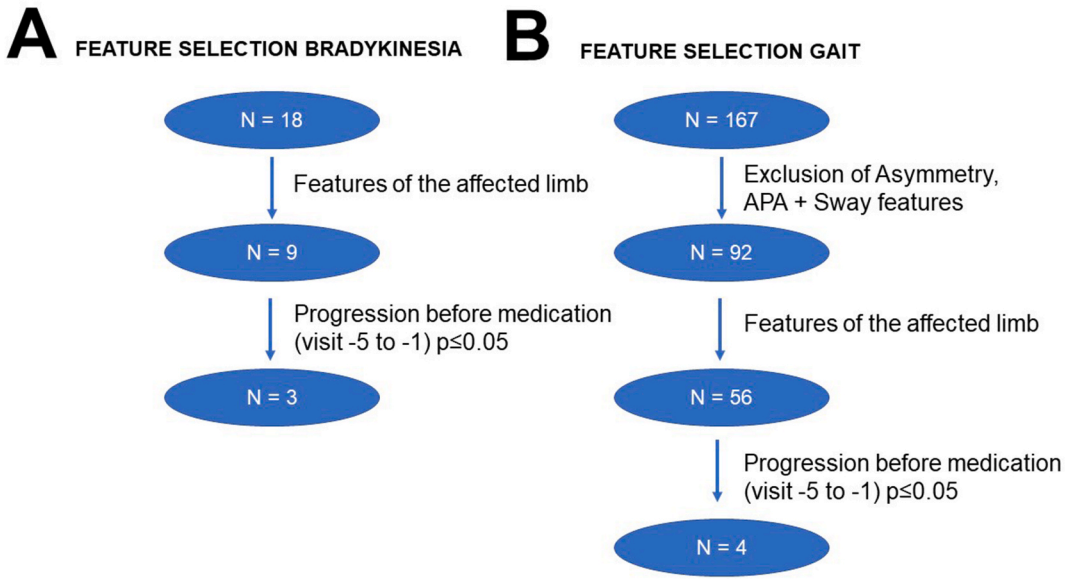

Fig. 4. Selection of the parameters included in the analysis of bradykinesia (A) and gait (B) features. APA = Anticipatory Postural Adjustments.

Table 3
Summary of antiparkinsonian medication commenced during the first on-medication visit of the study.

Patient no.	Medication	Dosage	Frequency (per day)
1	Co-careldopa	25mg/100 mg	3
2	Co-beneldopa	100mg/25 mg	3
3	Ropinirole	1 mg	1
4	Co-careldopa	12.5mg/50 mg	3
5	Ropinirole	0.25 mg	3
6	Co-beneldopa	50mg/12.5 mg	3
7	Ropinirole	0.25 mg	3

Additional information

No additional information is available for this paper.

Declaration of competing interest

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

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