UNIVERSITY OF OXFORD

QUANTIFYING BRADYKINESIA IN PARKINSON'S DISEASE



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Abstract

Parkinson's disease (PD) is a progressive, neurodegenerative disorder affecting more than 8.5 million people worldwide. It is characterized by a range of motor and non-motor symptoms resulting from the death of dopaminergic neurons in the subtantia nigra and the intraneural α-synuclein deposition. Despite extensive research into objective biomarkers, PD diagnosis and staging remain reliant on a subjective clinical assessment of symptoms using questionnaires and scales. This approach presents several limitations. Assessments are prone to intra- and inter-observer variability arising from human error and imprecision. With limited granularity, disease signal may only be detected once a significant portion of dopaminergic neurons are lost, thus making early detection and prevention very difficult.

Current treatment options include medical and surgical methods. Dopaminergic medication aims to replace the missing neurotransmitter, whereas deep brain stimulation works directly on the basal ganglia circuitry. Whilst very effective, these treatments do not affect disease progression. New disease-modifying agents are being proposed to alter or halt the neuropathology of PD. Unfortunately, their evaluation is hindered by the lack of precise and objective disease monitoring metrics. A sensitive biomarker could be crucial for research efforts through minimizing expenditure in evaluating ineffective drugs and thus allowing for a more optimised allocation of resources.

To that end, new technological solutions have been proposed, enabling rapid, accurate, non-invasive, and objective quantification of motor disturbances using wearable sensors. This thesis presents a study of the utility of such sensors in quantifying bradykinesia: a key diagnostic symptom of PD. It explores the use of machine learning algorithms and feature engineering to evaluate clinically important outcomes such as disease monitoring, medication response, fall likelihood, and quality of life decline. Finger tapping, hand movement, pronation supination, gait and balance measurements were taken from participants with PD every three months for up to two years. In addition, cross-sectional study of finger tapping was conducted on patients undergoing evaluation for deep brain stimulation. In this group, the on/off medication and on/off stimulation conditions were examined.

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Recurring Abbreviations

PD: Parkinson's Disease

DBS: Deep Brain Stimulation

IMU: Inertial Measurement Units

MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale

GPi: Globus Pallidus Interna

STN: Subthalamic Nucleus

DA: Dopamine

COMT: Catechol-O-Methyltransferase

MAO-B: Monoamine Oxidase B

MoCA: Montreal Cognitive Assessment

ROC-AUC: Receiver Operating Characteristic - Area Under Curve

RF: Random Forest

XGB: eXtreme Gradient Boosting

SVM: Support Vector Machine

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Introduction

Clinical Motivation

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting over 8.5 million people globally (WHO, 2022). The incidence of PD varies depending on environmental and genetic factors (Poewe et al., 2017), but it is estimated that approximately 17 in every 100,000 individuals will be diagnosed with the disease every year (Twelves et al., 2003). The global burden of PD is increasing faster than any other neurological disorder. The latest World Health Organisation (WHO) data show that PD-associated deaths more than doubled since 2000, resulting in 329,000 deaths and 5.8 million disability-adjusted life years per annum (WHO, 2022). PD itself may not significantly compromise life expectancy; however certain complications related to PD can contribute to mortality. These might include pneumonia, falls resulting in fractures, or other health issues that would not have arisen if not for PD. Since PD mainly affects people over the age of 50, its prevalence constitutes a significant factor in the healthcare needs of the ageing population (von Campenhausen et al., 2005).

PD is primarily classified as a movement disorder, but it can manifest as a multitude of motor, psychological and cognitive symptoms (Kalia and Lang, 2015). The classical presentation consists of bradykinesia (slowness of movement) in combination with rigidity or rest tremor (Postuma et al., 2015). Postural instability, fatigue, dyskinesias and hesitations are also frequently seen (Tolosa et al., 2006). Non-motor symptoms include diminished cognitive ability, apathy, depression, and sleep dysfunction (Chaudhuri and Schapira, 2009). Severe disability and dementia are more pronounced in the later stages of the disease, occurring in an estimated 40% of patients (Fahn, 2003). There is currently no cure for PD. All available treatment options are purely symptomatic and aim at lessening symptom severity and improving quality of life (Hayes, 2019). Novel therapeutic agents are being trialled with the hope of halting or reversing disease progression; however, no substance has been proven to achieve this in clinical trials (Ntetsika et al., 2021).

Clinical examination remains the mainstay of diagnosis, disease monitoring and research evaluation of Parkinsonian disorders (Beal et al., 2005; Bluett et al., 2021; Boxer et al., 2017; Burn, 2013; Coughlin and Litvan, 2020; Golbe, 2014; Golbe and Ohman-Strickland, 2007; Jankovic, 2008; Kobylecki, 2020; Rowe et al., 2021). A skilled physician conducts a series of tests and assigns scores according to well-established clinical rating scales (Goetz et al., 2007; Grötsch et al., 2021). Proficiency in this skill requires time, specialist knowledge and experience (Stone et al., 2005; Suri, 2021), often in a particular area of movement disorders (Burn, 2013). Thus, experts in the field are scarce and may reside in specialist centres that can be inaccessible to a significant part of the affected population (Nolen and Mejia, 2021). Furthermore, even the most trained eye may not be able to capture the full complexity of a particular disease presentation (Sarma, 2018). Studies show significant intra- and inter-rater variability (Heldman et al., 2014) and the limiting of granularity caused by rigid rating scales (Heldman et al., 2011). Thus, there is a pressing need for new clinical tools that could be used to improve patient selection and ensure that a new drug is offered to the right population, with meaningful outcome measures (Cedarbaum, 2018).

Digital sensors can provide quantitative and continuous measurements of symptoms at a level of detail that could not be feasible for a human assessor (FitzGerald et al., 2018; Hadley et al., 2021; Patel et al., 2023; Schalkamp et al., 2023). Symptoms such as gait, speech, cognition, and tremor could be captured through a series of digital tasks, thus reducing the subjectivity and variability of the current scoring systems (Antoniades et al., 2015; C. Antoniades et al., 2012; C. A. Antoniades et al., 2012; Czech et al., 2024; Dale et al., 2023; FitzGerald et al., 2018; Mancini and Horak, 2016; Mera et al., 2013; Sotirakis et al., 2023). These measurements can then be used to perform disease classification or severity prediction using machine learning techniques (Abate et al., 2023; Schalkamp et al., 2023; Sotirakis et al., 2023). Digital assessment can also be done remotely, thus extending the access to high-quality clinical measurement and research evaluation (Gray et al., 2020; Poleur et al., 2023). Many systems utilise wearable sensors in the form of gyroscopes and accelerometers, often in combination with devices known as inertial measurement units (IMUs) (Maetzler et al., 2013). So far, the literature has focused on cross-sectional analysis and technology piloting, with a few studies reporting real-life applications like PD population screening (Dlamini et al., 2021),

telemedicine clinics (Heldman et al., 2017a), or treatment response assessments (Espay et al., 2011; Heldman et al., 2014; Isaacson et al., 2019; Tamás et al., 2016). Larger longitudinal studies have only recently been reported (Sotirakis et al., 2023; Weiss et al., 2014).

Unfortunately, very few solutions have translated into routine clinical practice (Akram et al., 2022). This could be due to cost, difficult and time-consuming initial set-up, and lack of compelling clinical benefit. For many, a wearable device or a set of high-resolution computer vision cameras do not add enough information to be worth their cost and added time in clinic. More straightforward solutions, on the other hand, often lack accuracy due to low sampling rates, imprecise equipment, or human-related factors (vision impairment, technology learning curve). Another issue is the lack of transparency. Many devices use proprietary analytical algorithms and do not release schematics of the hardware, software algorithms, or raw data. This makes their generalisation very difficult (Morgan et al., 2020). The real-life uptake of these technologies depends on providing a convincing, explainable, and easy-to-use solution to actual problems seen in day-to-day clinical practice.

Research Objectives of the Thesis

This thesis will focus on objective measurement of bradykinesia – a common and cardinal symptom of PD. In particular, it will focus on investigating how digital devices can be used to evaluate clinically important outcomes: disease monitoring, reaction to medication, likelihood of experiencing falls, and decline in quality of life. The overall aim is to produce a digital measurement toolbox that could provide concrete and scientifically validated data for researchers, physicians, and patients alike. The results of the analysis submitted for examination could be used to inform clinical trials, health, and social care policies. Perhaps most importantly, this work will aim to provide informative data for personal decisions and much-needed answers for patients and carers who are living with the diseases examined by this thesis.

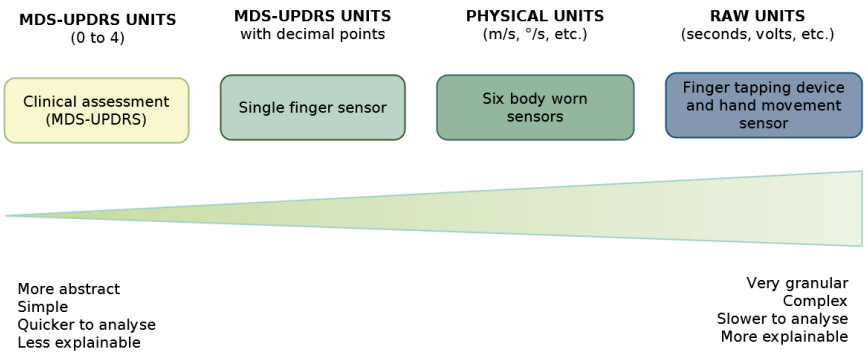


Figure 0.1 Increasing levels of granularity of signal provided by different sensor systems. The thesis will discuss this in increasing levels of complexity.

Structure of the Thesis

This thesis will examine the concept of quantification of bradykinesia in an increased order of complexity and granularity (Figure 0.1). The introductory chapter will set out a succinct clinical and pathological background to PD, with a focus on bradykinesia. It will be followed by a review of currently available clinical scales and digital assessment methods. Then, the problem of quantification of bradykinesia will be approached from the perspective of increasing order of complexity. Chapter 2 will present an evaluation of commercially available sensors utilised for standard clinical examination. This will be done by comparing measurements obtained by MDS-certified clinicians in a longitudinal study of medicated PD patients. Chapter 3 will focus on investigating whether the same single-finger sensor, along with a set of six body-worn IMUs, is able to reliably measure response to the introduction of antiparkinsonian medication. Chapter 4 investigates the problem of falls prediction in the PD population. Machine learning models will be trained on kinematic data to calculate the likelihood of experiencing a fall at 24- and 60-months' follow-up. Chapter 5 will focus on a novel finger tapping measurement device designed and engineered to work with bespoke analytical software. Feature engineering will be applied to the raw signal to assess clinically observable characteristics of bradykinesia. Changes in these features will be discussed in the context of ON/OFF medication and ON/OFF Deep Brain Stimulation (DBS) states. Finally, Chapter 6 concludes the thesis and discusses the results in the context of other work, limitations, and future research directions.

Outputs and summary of contributions

This section summarises the contributions made by various collaborators for each of the chapters in this thesis. Work submitted for publication is also noted.

Chapters 2 to 6 contain results from the Oxford Quantification in Parkinsonism (OxQUIP) study – a longitudinal study conducted at the John Radcliffe Hospital in Oxford. Although the candidate collected a substantial part of the data, it is important to acknowledge contributions from fellows, research assistants, project administrators, participants, family members, and careers who have committed countless hours to the collection and tabulation of data.

Chapter 2 – work from this chapter is currently in preparation for publication. CS provided statistical scrutiny and constructive criticism of analytical methods. GR & MP helped with the collection and tabulation of data.

Chapter 3 – results were submitted and published in *Helion (Cell Press)*. NC contributed to the analysis of six IMUs; CS helped design analytical methods.

Chapter 4 – results were submitted for publication in *NPJ Digital Health.* CS and SP contributed to the analysis of the IMUs and survival modelling.

Chapter 5 – DBS testing was conducted alongside routine Neuromodulation perioperative assessment service at the John Radcliffe Hospital in Oxford. The DBS specialist nurses Beth Petric, Claire Fletcher, and Laura Bacchini were indispensable in screening patients and helping with the complex logistics of testing.

CS = Dr Charalampos (Harris) Sotirakis, PhD

GR = Dr Gloria Romagnoli, PhD

MP = Dr Marta Pereira, PhD

NC = Mr Niall Conway, MSc

SP = Dr Salil Patel, BMBS MSc

1

Physiological Background to Bradykinesia in Parkinson's Disease

1.1 Pathophysiology of Parkinson's Disease

1.1.1 Neuropathological mechanisms

PD is characterised by two major neuropathological findings: the loss of pigmented dopaminergic neurons in the subtantia nigra pars compacta (Fearnley and Lees, 1991; Halliday et al., 2011) and progressive aggregation of α-synuclein (Surmeier, 2018). Death of dopaminergic neurons can be observed on slides of the midbrain, stained for tyrosine hydroxylase (rate-limiting enzyme for dopamine synthesis). Ventrolateral parts of the substantia nigra tend to be more affected, with sparing of medial and dorsal regions (Damier et al., 1999). α-Synuclein normally plays a benign role in synaptic vesicle dynamics, mitochondrial function, and intracellular trafficking of a healthy neuron (Vekrellis et al., 2011). Neurotoxicity begins when these 140 amino acid protein monomers form oligomers, protofibrils and eventually insoluble fibril aggregates in β-pleated sheets (Balupuri et al., 2019; Uversky and Eliezer, 2009). This accumulation of α-synuclein inside the nerve cells can be observed in the form of Lewy Bodies (inclusion bodies) under the microscope (Jellinger, 2007). Immunohistochemical staining reveals diffuse, granular, dot-like structures of intracytoplasmic depositions of α-synuclein (Uversky and Eliezer, 2009). Several potential causes of this abnormal accumulation have been identified. Deficits in overproduction, misfolding and oligomerization lead to increased neurotoxic load (Kaushik and Cuervo, 2015), whereas impaired autophagosome, ubiquitin–proteasome and lysosomal autophagy systems lead to ineffective removal of the toxic elements (Xilouri et al., 2013). Increasing age,

neuroinflammation and genetic mutations can all contribute to the acceleration of α-synuclein pathology (Moehle and West, 2015; Nalls et al., 2014; Ransohoff, 2016; Vekrellis et al., 2011). Mitochondrial dysfunction can also exacerbate α-Synuclein misfolding. Deficits have been observed in complex I, a part of the mitochondrial electron transport chain, PGC1α, a regulator of mitochondrial gene expression, and En1, PARK2, PIN1 and LRRK2 genes responsible for maintaining mitochondrial integrity (Bose and Beal, 2016; Nordström et al., 2015; Pickrell and Youle, 2015; Schapira, 2007). Dysfunction in these mitochondrial pathways leads to an increase in oxidative stress, which in turn propagates the depletion of lysosomes and lysosome-dependent degradation of β-pleated sheets (Alam et al., 1997; Dias et al., 2013). Nigral dopaminergic neurons can be particularly sensitive to oxidative stress, owing to their long unmyelinated axons and a large number of synapses (Bolam and Pissadaki, 2012). Maintenance of such a complex neuronal network requires an extensive energy supply (Pissadaki and Bolam, 2013). Thus, deficits in mitochondrial function, oxidative stress and calcium metabolism make subtantia nigra neurons particularly vulnerable (Dehay et al., 2010; Surmeier, 2018). Insulin also plays a role in PD pathophysiology by influencing brain insulin resistance, neuroprotection, cognitive functions, and mitochondrial function (Bassil et al., 2022). This is why people with type 2 diabetes may have an increased risk of developing PD, although this remains to be fully elucidated in large-scale clinical trials. Studies have shown that brain insulin resistance, indicated by altered insulin/IGF-1 signaling and phosphorylation of insulin receptor substrate-1, is present in PD patients and animal models (Bassil et al., 2022; Nowell et al., 2023) and can lead to increased α-synuclein aggregation, dopaminergic neural loss and autophagy dysfunction (Aviles-Olmos et al., 2013; Kakoty et al., 2023; Ruiz-Pozo et al., 2023). A graphical summary of these molecular processes is presented in Fig. 1.1.

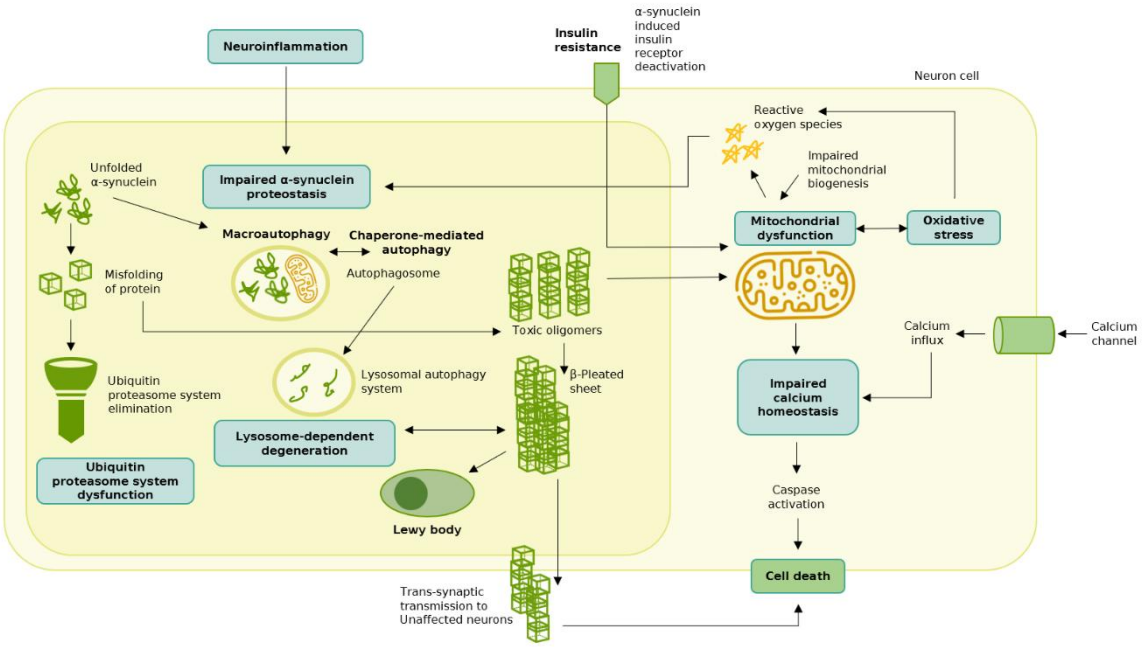


Figure 1.1 Summary of cellular neuropathological mechanisms leading to cell death and neurodegeneration in PD. Based on the review of cellular and molecular evidence in the pathogenesis of PD (Poewe et al., 2017; Ruiz-Pozo et al., 2023).

The extent of synucleinopathy in PD can be described using Braak staging (Braak et al., 2003) (Fig. 1.2). Braak and colleagues theorised that α-synuclein accumulation follows a prion-like anatomical path of progression. In stage I and II (asymptomatic), cholinergic and monoaminergic lower brainstem neurons are affected (Halliday and McCann, 2010). In stage III and IV, the disease progresses to midbrain and basal forebrain, and in stage V, Lewy bodies can be found in the temporal, parietal, and frontal regions as well as the vagus nerve and locus ceruleus (Ka, 2009). The final stage VI features a full invasion of motor and sensory areas of the brain, signalling the most severe cases of PD. This theory could explain the clinically observed progression of severity of PD symptoms in time.

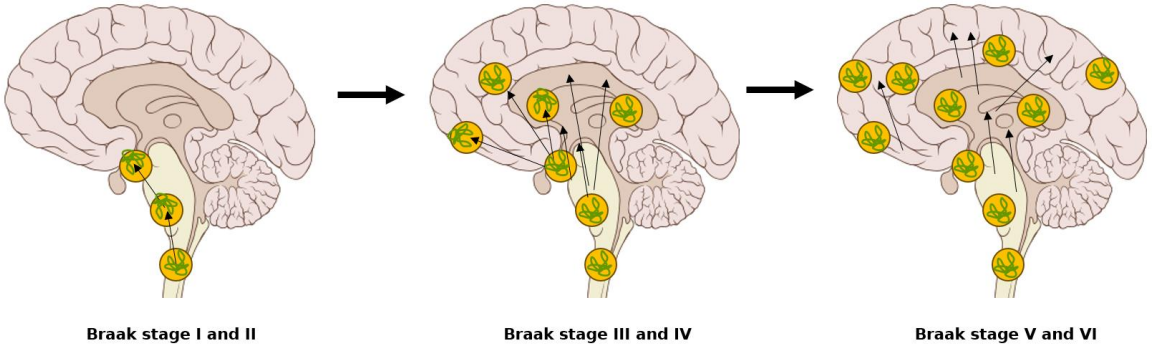


Figure 1.2 Braak staging reveals a spatiotemporal progression of α-synuclein aggregation in PD without Alzheimer's pathology. Initially, α-synuclein inclusions appear in cholinergic and monoaminergic neurons of the lower brainstem in asymptomatic individuals (stages I and II). As the disease progresses to motor stages (stages III and IV), aggregation extends to similar neurons in the midbrain and basal forebrain. Finally, in advanced stages (V and VI), α-synuclein pathology reaches limbic and neocortical regions, further reflecting disease spread.

1.1.2 Genetics

The majority of PD cases are sporadic, although more than 20 genes have been associated with early, severe, and atypical presentations (Blauwendraat et al., 2020). Monogenic PD is exceedingly rare (Klein and Westenberger, 2012) Examples include SNCA (Polymeropoulos et al., 1996), VPS35 (Wider et al., 2008), and PRKN/ PARK7/ PINK1 ("early-onset" family) (Kitada et al., 1998). These genes affect previously discussed molecular and metabolic pathways such as α-synuclein aggregation, lysosomal and mitochondrial dysfunction. Two major genes showing variable penetrance are LRRK2 and GBA. They may not demonstrate a classic Mendelian pattern of inheritance but can be considered genetic risk factors for developing PD (Alexander et al., 2004; Sidransky et al., 2009). Finally, there are many other alleles that exert a small but additive effect on PD traits. Genome-wide association studies (GWAS) studies identified these in cases of idiopathic PD, adding to the body of knowledge on pathophysiology and suggesting potential targets for future gene therapy (Yengo et al., 2018).

1.1.3 Environmental risk factors

Lifestyle, dietary and toxic exposure factors can influence the risk of developing PD (Ascherio and Schwarzschild, 2016; Noyce et al., 2012; Shan et al., 2023). Pesticides (Alberto

et al., 2006), manganese (Dayan and Arkadir, 2023; Guilarte and Gonzales, 2015), carbon disulfide (Ea and Sk, 2010), inorganic heavy metals (mercury, iron, copper, and lead) (Pyatha et al., 2022) and industrial solvent trichloroethylene (Dorsey et al., 2023) have all been implicated in increasing incidence of Parkinsonian symptoms. Ecological research suggests that exposure to these toxins may contribute to PD epidemics in countries with lower workers' protection and environmental pollution standards (Dorsey et al., 2018; Zheng et al., 2023). Exposure to some molecules and environmental factors seems to be protective against PD. Caffeine intake and exercise are the two most effective primary prevention and non-medical symptomatic improvement measures (Ernst et al., 2023). In the study of Health Professionals, maintaining regular (>10 months) strenuous physical activity conferred a relative risk reduction of up to 60% (Ascherio and Schwarzschild, 2016). Consuming three to four cups of coffee per day has been reliably shown to lower the risk of developing PD by up to 82% (Je and Giovannucci, 2014; Liu et al., 2012; Poole et al., 2017). Other protective substances have been suggested, although the evidence for their use is limited (flavonoids, statins, calcium channel blockers, specific dietary patterns) (Ascherio and Schwarzschild, 2016). Nicotine consumption through smoking or chewing tobacco has also been shown to offer neuroprotection (O'Reilly et al., 2005). It is thought that the risk-lowering effect of these substances is due to their anti-inflammatory properties (McKenzie et al., 2017). Interventional studies are underway to utilise this in prospective cohorts (Belvisi et al., 2020).

1.1.4 Clinical presentation

PD can manifest with a diverse range of signs and symptoms with varying degrees of severity and impact on the quality of life (Bloem et al., 2021; Naisby et al., 2021; Williams-Gray et al., 2013, 2009) (Fig. 1.3). Prodromal symptoms can start as early as 10 years before a formal diagnosis of PD (Heinzel et al., 2019). Patients report REM sleep behaviour disorder, hyposmia, anxiety, depression, fatigue, and constipation. These symptoms persist and intensify throughout the course of the disease. Apathy, pain, memory and executive function impairment, autonomic dysfunction (most notably orthostatic hypotension), urinary symptoms, and dysphagia have all been reported (Chen et al., 2020; Jankovic, 2008; Naisby et al., 2021). As the disease progresses, dyskinesias, on/off state fluctuations, and gait and posture

problems become more apparent(Mirelman et al., 2019). In the final stage of PD, falls and falls-associated disability can be compounded by severe cognitive deficits in the form of Parkinson's Disease Dementia (Williams-Gray et al., 2006).

It is important to note that not all cases of PD follow the same natural progression. Two main phenotypes can be identified: tremor-dominant and postural instability/gait difficulty, with distinct patterns of natural history and speed of progression (Prime et al., 2020; Zuo et al., 2017). Patients can also be grouped by the origin of pathology. A "body-first" and "brain-first" PD have been suggested (Horsager et al., 2022). According to this hypothesis, PD can be characterised on the basis of the point of initial insult (Borghammer, 2023; Borghammer et al., 2021; Horsager et al., 2022). If the toxic trigger begins in the nigral regions, patients experience milder, asymmetric, hypoosmic, and motor-dominant symptoms. If neurotoxicity begins in the gut, autonomic, symmetric, and cognitive symptoms prevail. With a prion-like spread of the pathology, symptomatic profiles of all phenotypes converge in the late, advanced stage of the disease (Borghammer and Van Den Berge, 2019).

The Movement Disorder Society (MDS) established diagnostic criteria to facilitate a systematic and reproducible clinical diagnosis of PD (Heinzel et al., 2019; Postuma et al., 2018, 2015). As per these criteria, a new diagnosis requires the presence of bradykinesia and at least one additional motor feature (rigidity or rest tremor) (Postuma et al., 2015). Clinicians are also further required to investigate several other diagnostic domains (Poewe et al., 2017). Criteria supporting the diagnosis are as follows: responsiveness to antiparkinsonian medication, presence of levodopa-associated dyskinesias, olfactory loss, cardiac sympathetic denervation (on metaiodobenzylguanidine [MIBG] scintigraphy) and presence of classic rest tremor. Alternative diagnoses should be sought through history taking, examination and neuroimaging. Diagnostic differentials include space occupying lesions, encephalopathy, atypical, drug-induced parkinsonism, and essential tremor. Finally, attention must be paid to the course of the disease during follow-up. Rapid progression of gait impairment, falls, or severe autonomic failure should prompt reconsideration of diagnosis (Burn, 2013; Greenland and Barker, 2018).

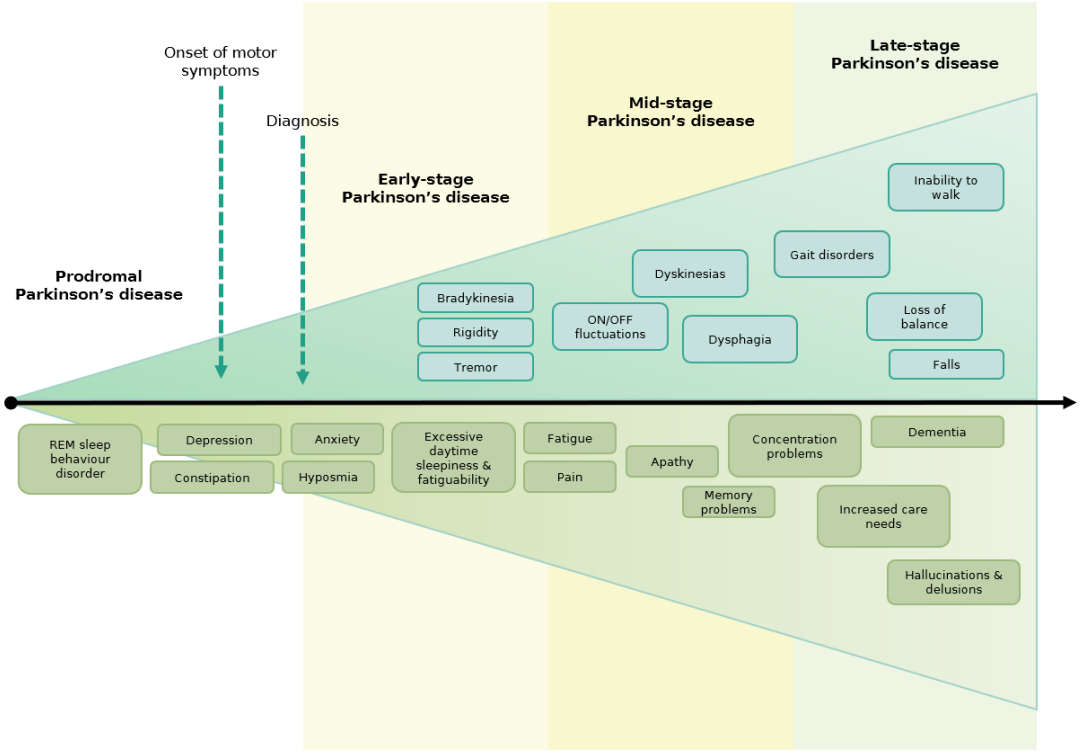


Figure 1.3 Timeline of symptoms onset and severity in PD. Upper triangle shows motor, lower non-motor symptoms. Non-specific complaints such as REM sleep behaviour disorder, hyposmia and depression can precede PD diagnosis by years. Official diagnosis of PD is usually made after at least several months of motor symptoms. Health and social care needs intensify towards the end of life, when some patients become severely disabled, with poor response to levodopa and increased side effects of polypharmacy. Based on (Poewe et al., 2017).

1.1.5 Diagnosis and biomarkers

The field of biomarkers and objective diagnosis of PD has accelerated over the last three decades. The only currently widely accepted neuroimaging investigation is the 123I-ioflupane single-photon emission CT (SPECT) (also known as DaTscan) (de la Fuente-Fernández, 2012; Scherfler et al., 2007). It can help distinguish PD from similarly presenting diseases by showing distinct presynaptic nigrostriatal terminal dysfunction (Stoessl et al., 2014). Standard MR imaging can also give important structural insights by excluding tumours, cerebral ischaemia or inflammatory diseases as differential diagnoses (Mahlknecht et al., 2010). PET or SPECT scans with noradrenergic tracers can also be utilised in scanning the myocardial nervous system. Sympathetic denervation of the myocardium is rarely seen in atypical Parkinsonism, and thus can form an important diagnostic cue in PD.

A range of other experimental diagnostic investigations have been proposed. These can be loosely grouped into physiological, genetics, blood, and cerebrospinal fluid (CSF) studies. Genetic testing is becoming increasingly common. Mono and polygenic mutations discussed earlier in this chapter (SNCA, LRRK2, GBA1, PRKN, PINK1 and others) can be tested in specific clinical scenarios of significant familial or ethnic history of PD (Pal et al., 2023). Prompts for genetic testing usually include families with multiple affected members, history of consanguinity, populations with known high mutation frequencies (e.g. Ashkenazi Jews, North African Arab Berbers), atypical or early presentation (disease onset <50 years of age) (Di Fonzo et al., 2018; Falcone et al., 2011). CSF and blood analysis have not yet been validated for routine clinical use, although several potential diagnostic and prognostic indices have been suggested. Most frequently studied are: α-synuclein species, lysosomal enzymes, markers of amyloid and tau pathology, and neurofilament light chain (Parnetti et al., 2019). The alpha-synuclein seeing assay has been most widely supported for the first routine blood test in the differential diagnosis of PD (Fernandes Gomes et al., 2023). Physiological biomarkers encompass a wide range of wearable sensors and apps that can measure walking patterns, tremor, rigidity, and sleep behaviour disturbances (Brognara et al., 2019; Espay et al., 2016; Ko et al., 2022). Although none have yet been approved for diagnosis or prognostication, clinicians often use them for medication changes, DBS settings, and physiotherapy evaluation (Gordt et al., 2018; Su et al., 2023; Watts et al., 2021; Wu et al., 2020). Physiological digital measurement tools pertaining to quantification of bradykinesia will be discussed in detail in relevant chapters.

1.1.6 Management options

Treatment of PD is currently only symptomatic (Yuan et al., 2010). Levodopa and dopamine receptor agonists have been the mainstay of medical management. Since their inception in the late 1950s, advances have been made in terms of improving pharmacokinetics, ease of delivery and tolerability. Modern treatment schedules can thus involve a finely tuned range of immediate and modified release preparations, along with intelligent modes of delivery (e.g. through pumps, gels or app-based timings) (Gupta et al., 2019; Nilsson et al., 2001; Nyholm et al., 2020; Tang et al., 2023; Urso et al., 2020). A full discussion of dopaminergic

medical treatment options and their effect on PD physiology is presented in Chapter 3. The medications that do not primarily target dopamine but aim to reduce its breakdown include Monoamine Oxidase B (MAO-B) inhibitors such as selegiline and rasagiline, and Catechol-o-methyltransferase (COMT) inhibitors such as entacapone and opicapone (Regensburger et al., 2023). Adenosine A_{2A} receptor antagonists such as istradefylline are a newer class of medication for improving motor symptoms in the "off' dopamine state (Cabreira et al., 2019). They utilise the synergistic localisation of adenosine A_{2A} and dopamine D2 receptors in the striatum (Cieślak et al., 2008). Istradefylline is currently only approved for use in the US and Japan (Takahashi et al., 2022) and its market authorisation in the EU has been denied. Amantadine and anticholinergic medication are sometimes used for tremor or dyskinesias, though this is only recommended once other options have been exhausted (NICE, 2017). Supplementary medical therapy can also be initiated for PD-associated depression, anxiety, apathy, dysphagia, sleep disorders, pain, muscle spasms, hallucinations, or hypotension. This, unfortunately, often leads to polypharmacy and requires complex medical decision-making (Csoti et al., 2019).

There is a plethora of new drug candidates currently investigated for PD. The most comprehensive list – the "Parkinson's Hope List", maintained by Dr Kevin McFarthing, a biochemist and a person living with PD – contains 220 pre-clinical and 163 clinical candidates, as of March 2024. There is a shifting paradigm in therapeutic agents for PD, as four disease modifiers have successfully progressed in phase III of clinical trials. These include one repurposed drug (GLP-1 agonist, exenatide) and three new chemical entities: alpha synuclein translation inhibitor, LRRK2 inhibitor and Gcase enhancer aimed to improve lysosomal function (McFarthing, 2024). Other potential therapeutic agents include a multitude of repurposed or reformulated drugs for symptomatic relief, stem cells, neural transplantation, and gene therapies.

Surgical treatment options include ablation or stimulation of selected anatomical targets (Subthalamic nucleus (STN), Globus Pallidus interna (GPi), pedunculopontine nucleus (PPN)) (Betchen and Kaplitt, 2003). Thalamic DBS can be offered to patients with predominantly severe and disabling tremor (Cury et al., 2017). Though life-changing, this therapy is currently only available for well-selected population, for whom it may provide the largest symptomatic relief. The effects of DBS will be discussed in more detail in Chapter 5.

Non-medical treatment includes physiotherapy, targeted exercise programmes (e.g. FIGHT-PD (Blacker et al., 2024)), sports, strength training, speech and language, dietary and supplement interventions (IQWiG, 2019; Okada et al., 2021; Tomlinson et al., 2012). It is important to note that as PD is a highly variable disease, treatment options need to be tailored to the individual living with the disease and evaluated against patient priorities and quality of life, as well as "objective" medical tests and scales.

1.2 Neurophysiological characteristics of bradykinesia in PD

1.2.1 Neural circuitry organisation

Execution of normal motor control is a learned process dependent on the coordination of the musculoskeletal and nervous systems (Roland, 1984). A significant portion of the brain is dedicated to this task. The motor cortex receives direct and indirect inputs from basal ganglia, cerebellum, and supplementary motor areas, which program and modulate movement execution. The supplementary motor area (SMA) is tasked with the preparation and selection of movement, pre-SMA modifies movement depending on cognitive, sensory and motivational inputs, whereas motor cingulate integrates response to pain, attentional and arousal states (Battaglia-Mayer and Caminiti, 2019; Egger et al., 2020; Muratori et al., 2013). Primary motor cortex also receives inputs from dorsal premotor (visual signalling, eye movements) (Ninomiya et al., 2019) and ventral premotor cortices (visuospatial perception) (Hoshi and Tanji, 2007). Command signals from the motor cortex are then sent through descending pathways to activate α-motor neurons. These units directly innervate skeletal muscles and represent the final common pathway through which movement is executed (Burn, 2013; Dum and Strick, 2002).

1.2.2 Clinical picture

The clinically observed slowness of movement is a result of several deficits found on different levels of this anatomical organisation (Bologna et al., 2018; Herz and Brown, 2023). In PD, bradykinesia manifests as reduced amplitude, speed, and accuracy of movement, particularly evident in repetitive and sequential tasks (Hong et al., 2024). Progressive slowness

and diminishing excursion angles reflect impaired cortico-basal-thalamocortical loops and striatal-pallidal dysfunction (Cutsuridis, 2019). Sensory modulation, cognitive state, and emotional factors contribute to fatigability and freezing of gait (Cutsuridis, 2018). Levodopa, by augmenting striatal dopamine, transiently ameliorates these symptoms, with efficacy waning over time and across movement types (Suppa et al., 2017). The neuropathological and physiological characteristics of bradykinesia in these two disorders will now be discussed in detail.

1.3 Central bradykinetic mechanisms

1.3.1 Movement programming

Patients with PD exhibit significantly prolonged reaction times even in seemingly simple tasks with predetermined responses (Heilman et al., 1976). This is most likely due to deficits within the programming stage, specifically in movement selection (Pascual-Leone et al., 1994; Pullman et al., 1988). Underactivity in the supplementary motor area (SMA) has been implicated in difficulties in integrating movement commands (Escola et al., 2003). Neuronal activity in the SMA is impaired in PD, with a decrease in response to visual cues and a diminished activity after the Go signal (Kübel et al., 2018). Abnormalities in movement-related potentials in PD subjects indicate a disruption in internal control mechanisms mediated by the SMA, leading to a reliance on external cues for movement guidance (Cunnington et al., 1995). These findings suggest that underactivity in the SMA contributes to difficulties in integrating movement commands in PD, particularly in internally determined movements.(Siciliano et al., 2020).

PD patients also initiate movement before the entire response sequence is prepared, suggesting discoordination between programming and execution (Jennings, 1995). This is further supported by increased activity in lateral premotor areas, hinting at compensatory mechanisms, attempting to overcome the delays in the supplementary motor area (Potgieser et al., 2014; Samuel et al., 1997). The Bereitschaftspotential (BP), a signature pre-movement EEG signal elucidates this in two components: BP1 reflecting SMA activity and BP2 involving

lateral premotor areas. In PD, the early BP1 component is often diminished with a later and larger BP2, suggesting compensatory overactivity in lateral premotor areas (Jahanshahi et al., 1995). Event-related desynchronization (ERD), another EEG measure of cortical activation, reveals further clues about the altered motor cortical engagement in PD. The duration of ERD before movement is shorter in PD patients, and the pattern of alpha and beta rhythm attenuation during movement is abnormal (Kühn et al., 2004). These discrepancies suggest a fundamental alteration in the way the cortex engages in both movement preparation and execution. Interestingly, dopaminergic stimulation can restore these normal patterns, highlighting its role in optimizing cortical engagement and facilitating smoother movement execution (Wang et al., 1999). This dynamic interplay underscores the central motor attempts to adapt and overcome deficits within the programming circuitry and shows that bradykinesia can be at least partially explained by failure in the central programming of motor responses (Berardelli et al., 2001).

1.3.2 Sensorimotor integration

Abnormalities in proprioception, two-point discrimination, and sensorimotor integration contribute to difficulties in scaling motor output and generating appropriate grip force (Demirci et al., 1997; Klockgether et al., 1995; Schneider et al., 1986). This disrupts the coordination of perception and responding to stimuli, leading to imprecise movements and challenges in manipulating objects. Impaired sensorimotor integration can also be inferred from the reduced contingent negative variation amplitude observed in EEG signals (Tzvetanov et al., 2022). This suggests difficulties in preparing for forthcoming movements based on anticipatory cues, potentially reflecting disrupted preparatory processes in the neural networks spanning the motor cortex, supplementary and pre- supplementary motor cortex, posterior parietal cortex, prefrontal cortex and anterior cingulate (Disbrow et al., 2022). Similar challenges are observed in cognitive and combined cognitive-motor tasks (Johansson et al., 2023; Xiao et al., 2023). Two potential explanations emerge: either a limited processing resource restricts multitasking, or an inherent difficulty in switching resources between tasks (Mittelstädt et al., 2022b, 2022a; Reiser et al., 2021). Additionally, patients might over-allocate

resources to compensate for basal ganglia deficits, leading to a performance decline when multiple demands compete for attention (Pilgrim et al., 2021; Weber et al., 2021).

1.3.3 Cerebellar inputs

There is growing evidence that the cerebellum plays a significant role in the pathophysiology of bradykinesia in PD. Deficits in cerebellar signalling may contribute to both the motor symptoms and compensatory mechanisms associated with the disease (Mirdamadi, 2016). Recent studies in non-human primates revealed reciprocal connections between basal ganglia and cerebellum via the thalamus and pontine nucleus (Bostan et al., 2013). Altered cerebellar activation can also be observed in humans during motor execution, learning, and even at rest, as revealed by neuroimaging studies (Wu and Hallett, 2013). The cerebellum is also reported to be involved in the modulation of tremor amplitude via cerebello-thalamo-cortical circuits (Zhong et al., 2022). This further potentiates bradykinesia through restriction of range and speed of movement (Brown et al., 1997; Logigian et al., 1991).

1.3.4 Motor circuit pathology - PD

The thalamo–cortico–basal ganglia circuits are an anatomically distinct but functionally connected group of brain structures responsible for the control of actions and goal-directed behaviour (Fig. 1.4,5). Four main circuits connect frontal cortical areas with corresponding regions of the thalamus and basal ganglia: limbic, prefrontal-associative, oculomotor and motor (Alexander et al., 1991, p. 6, 1986; Lanciego et al., 2012). In PD, signalling in these pathways is deficient, which manifests in several motor and non-motor symptoms (Milardi et al., 2019). Decreased dopaminergic activity in the striatum from the Substantia Nigra Pars Compacta modulates the “direct” and “indirect” pathways. This results in an increased GABA mediated inhibition of further thalamocortical projections and a reciprocal loss of motor cortex output (a “filter-like” function of the circuit). Bradykinesia is thought to arise this way, as an increase of aberrant signalling, rather than a loss of function phenomenon. DBS to GPi and STN improves bradykinesia in animals and humans by alleviating the inhibitory effect of these inputs, which proves this hypothesis (Bergman et al., 1990; Dostrovsky and Lozano, 2002; Laitinen et al., 1992). A “hyperdirect pathway” has also been identified. This circuit connects

the motor cortex and the STN and plays an important role in alleviating akinesia in DBS-STN treatment (Li et al., 2012). Other circuits, such as pre-frontal, associative, oculomotor, and limbic regions provide sensory and cognitive information to successfully execute movements in the context of more complex tasks (Alexander et al., 1991). Intrinsic pathologies in motor cortex excitability and plasticity are also observed (Bologna et al., 2018). Changes in connectivity between the cerebellum and basal ganglia may be important in tremor (Dirkx et al., 2016), whereas deficits in gait and balance could originate from abnormal basal ganglia output via projections into pedunculopontine and cuneiform nuclei (Windels et al., 2015).

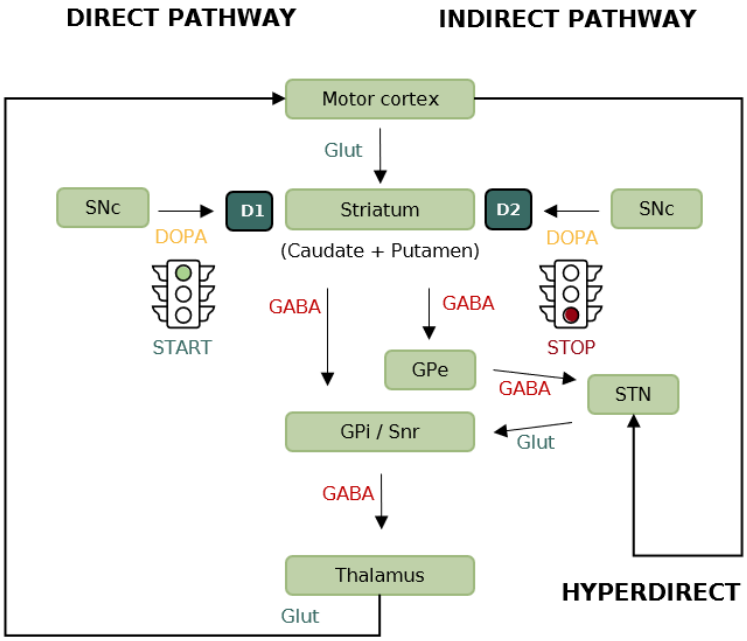


Figure 1.4. Main motor pathways in the basal ganglia. In healthy people, when dopamine levels are adequate, the direct pathway is active and stimulates the GPi and SNr. This inhibits the thalamus, which ultimately reduces inhibition on the motor cortex, facilitating smooth and coordinated movements. In PD, the dopamine levels are low direct pathway becomes less active and the indirect pathway becomes more dominant. This disinhibition of the STN leads to increased inhibition of the GPI and SNr, ultimately causing excessive inhibition of the thalamus and reduction of excitatory signals to the motor cortex. This impairs movement initiation and execution, leading to the characteristic symptoms of PD, such as tremor, rigidity, and bradykinesia. Hyperdirect pathways

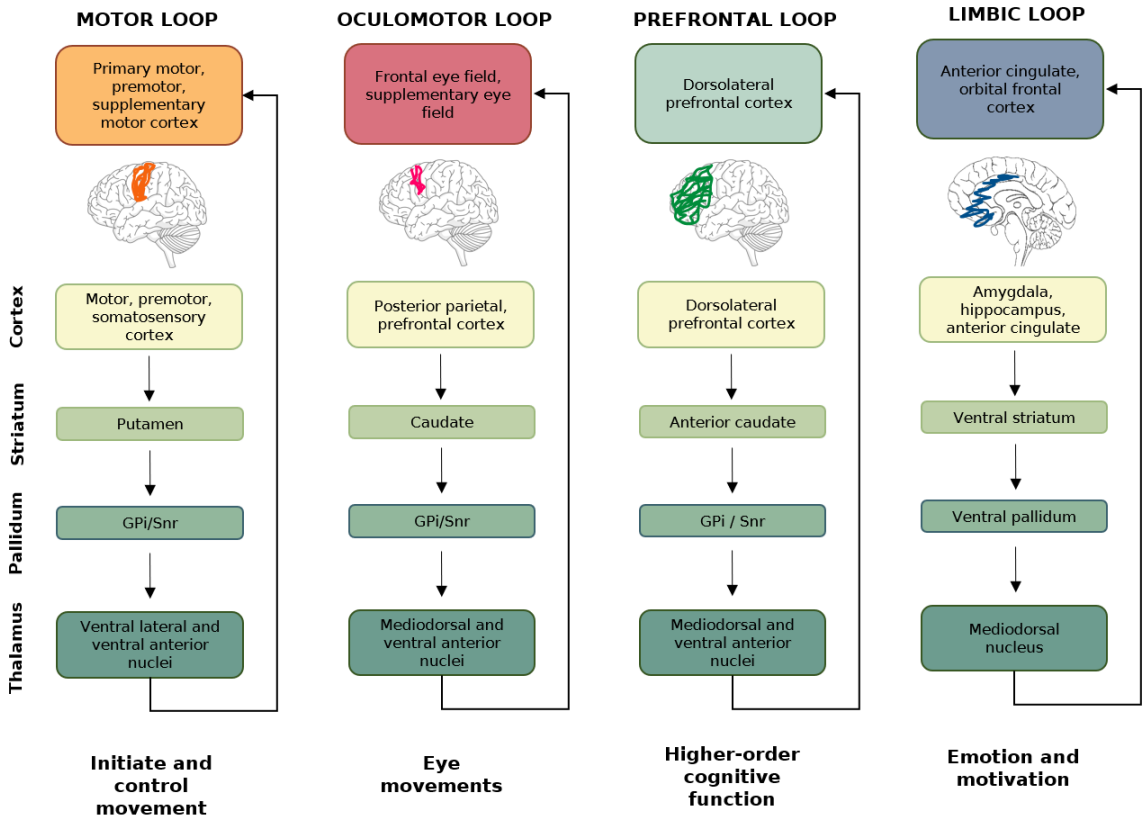


Figure 1.5 The parallel motor, oculomotor, associative, and limbic circuits of the basal ganglia. GPi = Globus pallidus interna, Snr = Substantia Nigra. Figure based on (Alexander et al., 1986).

1.4 Secondary factors

Central motor and basal ganglia mechanisms are the main pathological mechanisms of bradykinesia in PD. It is also important to consider secondary inputs that can modulate the slowness of movement. There are several major factors contributing to bradykinesia, which will now be discussed.

1.4.1 Muscle weakness

Studies dating back to the late 1980s have documented mild reductions in muscle strength across various muscle groups in PD patients compared to healthy controls (Stelmach & Worringham, 1988; Stelmach et al., 1989; Jordan et al., 1992). However, the findings have not always been consistent, likely due to challenges in controlling for factors like daily exercise and diet between patient and control groups. A study by Corcos et al. (1996) shed light on this

issue by measuring elbow strength in PD patients both "ON" and "OFF" L-dopa medication after overnight withdrawal. They found a 30% reduction in maximum elbow extension strength and a 10% decrease in flexion when patients were OFF medication. This observation suggests that the strength deficit is not due to intrinsic muscle properties changing overnight but rather to a reduced ability to maximally activate the muscles. Notably, the patients in this study seemed highly motivated to perform the tasks and there was no obvious lack of effort observed by the examiners. Physiological differences in EMG readings suggest that voluntary drive is not organised in the same way. Patients with PD seem to have reduced muscle power compared to age-matched controls and this may contribute to their global bradykinesia.

1.4.2 Rigidity

While rigidity seems intuitively linked to the slowness of movement (bradykinesia) observed in PD, its role remains complex and unproven. Evidence supporting a potential link comes from studies demonstrating enhanced long-latency stretch reflexes in PD patients (Tatton & Lee, 1975; Berardelli et al., 1983; Rothwell et al., 1983). These reflexes, triggered by muscle stretch, could theoretically contribute to bradykinesia by opposing the desired movement in antagonist muscles. To investigate this hypothesis, Johnson et al. (1991) employed a torque motor to unexpectedly stretch muscles during controlled wrist movements in PD patients. They found that reflex suppression in the antagonist muscle was weaker compared to healthy individuals, and this weakness correlated with the severity of bradykinesia.

A critical observation cast doubt on the antagonist co-contraction explanation. The study revealed that the level of antagonist muscle activity during unperturbed movements was no higher in PD patients than in healthy controls. This suggests that co-contraction might not be a significant limiting factor in bradykinesia, even for rapid movements where muscle activity patterns have been extensively studied. Despite the findings on enhanced stretch reflexes and their potential influence on antagonist muscles, the conclusive link between rigidity and bradykinesia remains elusive.

1.4.3 Rest and action tremor

Tremors in PD exert a multifaceted influence on movement execution, impacting both timing and speed. Studies by Hallett et al. (1977) and Wierzbicka et al. (1993) revealed a temporal coupling between tremor and movement initiation in PD. Patients tend to synchronize the onset of agonist muscle activity with the peak of their ongoing tremor, effectively delaying the intended movement's commencement. This subtle delay, iterated across multiple actions, can significantly influence overall reaction time.

The influence of tremor extends beyond the initiation of movement. Logigian et al. (1991) demonstrated that repetitive movements in PD can become "entrained" by action tremor, meaning the tremor's rhythm dictates the intended action's pace. The extent of this entrainment is directly proportional to the amplitude of the ongoing tremor. Higher tremor amplitudes exert a stronger influence on voluntary movement speed, leading to slower and more jerky movements. This underscores the critical role of tremor control in managing bradykinesia and improving overall motor function in PD.

Further investigations by Brown et al. (1997) revealed that persistent action tremor can contribute to muscle weakness during maximal contraction. This tremor, typically around 10 Hz in patients OFF medication, disrupts the smooth fusion of individual motor unit contractions, leading to reduced force output. However, a tremor itself cannot explain the strength decrease observed in all muscle groups, indicating the involvement of additional, likely central nervous system-related factors. The body of evidence indicated that rest and action tremors in PD are not merely contributors to muscle weakness; they represent a distinct dimension of motor impairment, exerting a profound influence on both movement initiation and speed.

1.4.4 Movement variability

Several studies demonstrated a reduced movement accuracy in PD, especially during fast movements (Sanes (1985), Sheridan and Flowers (1990), and Phillips et al. (1994)), suggesting a less efficient "speed-accuracy trade-off" compared to healthy individuals. An intriguing explanation offered by Sheridan et al. is that bradykinesia can be a deliberate strategy to prioritize accuracy. By slowing down, patients may attempt to compensate for impaired motor

control and ensure more precise movements. While this holds logical appeal, other factors seem to be at play too. Teasdale et al. (1990) observed persistent bradykinesia even in tasks where accuracy was no longer a critical factor, suggesting that the neuropathological picture is more complex. Understanding the reduced movement accuracy in Parkinson's disease requires considering both potential strategic adaptations and underlying motor control deficits.

1.4.5 Movement execution

Generating fast single-joint movements can be particularly challenging for patients with PD. This is at least in part due to the inability to produce an adequate initial agonist muscle burst, resulting in insufficient force to reach the intended target (Hallett et al., 1977). Completing the movement often requires a series of small-amplitude adjustments characterized by repetitive bursts of both agonist and antagonist muscles, or even prolonged continuous muscle activation (Baroni et al., 1984). Interestingly, despite this deficit, patients can increase the size of the initial agonist burst when aiming for larger movements. This compensatory mechanism highlights a specific issue with scaling dynamic muscle forces, known as the "scaling effect" (Pfann et al., 2001). Experimental evidence shows that this inappropriate scaling, rather than a global inability to generate force, plays a key role in the peripheral execution of motor tasks (Seidler et al., 2001). Complex, multi-joint movements are also disrupted. This is especially evident when comparing the execution times of two separate but simpler tasks vs a complex hand or arm movement (e.g. reaching, grasping, drinking, drawing) (Castiello and Bennett, 1997; Farley et al., 2004).

As movement complexity increases, bradykinesia becomes even more pronounced (Georgiou et al., 1994). Simultaneous or sequential movements are not only slower but also exhibit prolonged pauses between elements, suggesting difficulties in integrating and executing multiple movement sequences (Benecke et al., 1986). This is particularly pronounced when relying on internal control processes, as compared to externally cued movements (Currà et al., 1997). Visual or auditory prompts can effectively bypass the basal ganglia circuitry defects, resulting in improved gait characteristics (Redgrave et al., 2010). This goal-directed motor control is relied on extensively in moderate to severe disease (Nonnekes et al., 2019).

A prominent feature of bradykinesia is the sequence effect, a progressive decrement in movement speed and amplitude during repetition (Agostino et al., 1992). This manifests as progressive slowing in tasks like finger tapping, writing, and walking, potentially culminating in the freezing of gait (Iansek et al., 2006). Interestingly, the sequence effect appears less frequent in advanced PD compared to PD patients with preserved amplitude generation (Bologna et al., 2018; Djurić-Jovičić et al., 2016). One possible explanation for the lack of progressive slowing in these cases could be that the initial EMG burst is already at a low amplitude, thus exhibiting a floor effect (Bologna et al., 2018). The sequence effect may thus be absent in advanced cases, though not universally (Bologna et al., 2020). Levodopa, while improving movement speed and amplitude, generally fails to normalize the sequence effect (Espay et al., 2011; Suppa et al., 2017).

1.4.6 Central pattern generator

Rhythmic motor patterns, such as finger tapping, walking, scratching, and breathing, exhibit a unique combination of stereotypy and complexity while remaining under continuous voluntary control. Brown (1914) was the first to propose the existence of rhythmic central circuits, now known as central pattern generators (CPGs), responsible for the alternating flexion and extension of leg muscles during walking. He demonstrated this in decerebrated cats, showing they could generate sustained rhythmic locomotion without supraspinal or sensory input (Brown, 1914). Subsequent research revealed the requirement of both CPG activation and regions responsible for muscle tone generation in rhythmic locomotion (Takakusaki et al., 2008). Both CPGs, responsible for movement coordination and muscle tone regions, are located within the brainstem and spinal cord. Their activity is modulated by integrating afferent inputs from brain regions involved in motor and autonomic function (Grillner and Wallén, 1985). Little is known about the effect of CPG mechanisms on disruptions of repetitive movements in PD. In fact, experimental data suggest that these pacing signals are intact, at least in swallow control (Ertekin et al., 2002).

1.5 Outstanding research questions

Bradykinesia is a complex clinical symptom emerging from a range of PD-related neurophysiological deficits. The core pathophysiology involves dopaminergic depletion in the substantia nigra, leading to aberrant signalling through direct, indirect, and hyperdirect pathways. This central pathology, combined with impairments in central motor programming and sensorimotor integration as well as a range of peripheral secondary factors, manifests clinically as reduced amplitude, speed, and accuracy of movement. While clinical examination has long been the cornerstone of assessment, it faces inherent limitations: inter- and intra-rater variability, constrained granularity from rigid rating scales, and reliance on specialist expertise that may be inaccessible to many patients. These limitations are particularly challenging given bradykinesia's complex phenomenology, which includes sequence effects, variable medication responses, and interactions with secondary factors such as muscle weakness, tremor, and movement variability.

Digital quantification methods offer a promising solution through objective, continuous measurements of motor performance. However, despite technological advances, a significant gap remains between clinical needs and validated solutions. Current devices often suffer from practical constraints: complex technical requirements, limited cost-effectiveness, and proprietary algorithms that hinder independent validation and generalization. Furthermore, while preliminary digital assessment tools show promise, robust validation studies of their clinical utility remain scarce.

These challenges motivate several critical research questions: (1) How can existing commercial sensor systems be optimized for quantification of bradykinesia in standardised clinical examination? (2) What is the reliability and validity of sensor-based measurements in detecting response to dopaminergic therapy? (3) Can machine learning models trained on kinematic data predict clinically significant outcomes such as falls? (4) How can novel measurement devices be engineered to capture specific characteristics of bradykinesia in perioperative assessment of patients undergoing DBS assessment? Addressing these questions is fundamental to developing an evidence-based digital assessment framework that could provide robust, clinically meaningful data while maintaining feasibility for routine implementation in both research and clinical settings.

2

Wearable Sensors Automate Assessment of Upper Body Bradykinesia in Parkinson's Disease

2.1 Introduction

2.1.1 Clinical assessment of bradykinesia - current standard

As established in the previous chapter, bradykinesia is a hallmark feature of PD. It manifests as a reduction in the speed, amplitude, or rhythm of movement, and remains an essential criterion for PD diagnosis according to the International MDS guidelines (Postuma et al., 2015). Bradykinesia evaluation relies primarily on clinical examination. Traditionally, this method involved a trained clinician assessing patients through a series of tasks and questions, after which a global descriptive picture was produced, often in a form of a clinical letter (Burn, 2013).

To standardise this assessment, multiple scales have been developed (Table 2.1). The MDS Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is the most widely used tool (Goetz et al., 2008; Martínez-Martín et al., 1994) and is considered the "gold standard" for clinical trials. The third part of MDS-UPDRS consists of 18 items measuring the severity of distal and axial motor signs. Scores are assigned on an ordinal scale from 0 (asymptomatic) to 4 (severe) (Goetz et al., 2007). Finger tapping, hand opening, pronation-supination, toe tapping, leg agility, arising from a chair, gait and global body hypokinesia items are of specific interest in bradykinesia assessment (Pal and Goetz, 2013).

Table 2.1 Summary of currently used clinical rating scales for Bradykinesia Assessment in Parkinson's Disease.

Scale	Features	Strengths	Weaknesses	Applications	References
MDS-UPDRS	Most comprehensive, assesses motor and non-motor symptoms, good responsiveness to change	Standardized, sensitive, reliable	Time-consuming, complex scoring	Clinical trials, research, assessing response to treatment	(Goetz et al., 2007)
MBRS	Focuses on bradykinesia, provides more nuanced picture of individual characteristics	Easy to use, reliable	Limited scope, doesn't assess other motor or non-motor symptoms	Screening for bradykinesia, clinical practice	(Heldman et al., 2011)
CIS-PD	Overall disease severity rating by clinician	Global assessment, easy to use	Subjective, not standardized	Clinical practice, assessing disease progression	(Martínez-Martín et al., 2009)
PDQ-39	Patient-reported questionnaire on PD symptoms and impact on daily life	Patient perspective, comprehensive, good quality of life assessment	Requires patient self-report, may not be reliable in advanced stages	Assessing impact of PD on daily life, clinical trials	(Peto et al., 1995)
Hoehn and Yahr severity	Simple staging system for motor severity	Easy to use, well-known	Limited detail, doesn't assess non-motor symptoms	Clinical practice, assessing disease progression	(Hoehn and Yahr, 1967)
European PDCS	Simple scale for motor symptoms, good for clinical trials	Fast, easy to use, standardized	Limited scope, doesn't assess non-motor symptoms	Clinical trials, initial assessment	(Stocchi et al., 2018)

MDS-UPDRS requires extensive training and certification (Goetz et al., 2010). For each item, a clinician is tasked with observing repeated movements in a very short time frame. There are strict criteria for assessing changes in several categories, and additional rules for final score evaluation. This requires rapid integration of several observable features into a single metric, which may be difficult even for a highly trained and experienced physician. Subjective appraisals are inevitable and often lead to inter- and intra-rater variability (Chiang et al., 2016; Heldman et al., 2011). Clinical assessment is also impractical for frequent sampling required for optimisation of therapy or home monitoring studies (Cubo et al., 2017; Espay et al., 2016; Goetz et al., 2009; Heldman et al., 2017b; Mera et al., 2012). It is difficult to source enough expert clinician time to see patients at desired intervals, and access to specialist centres may be logistically challenging (FitzGerald et al., 2018). Innovations such as large-scale remote

clinical trials or data-driven treatment changes could bring immense benefits, which are currently inaccessible due to lack of scalability of manual MDS-UPDRS assessment. An automated, sensor-based solution, that provided the same or similar information via computerised analysis could streamline this process.

2.1.2 Sensor-based assessment

Several digital technologies have been proposed to automate MDS-UPDRS assessment. These can be broadly categorised into touchpads, gyroscopes, accelerometers, magnetometers, electromagnetic and inertial measurement units (for a comprehensive review, see (Maetzler et al., 2013)). More recently, smartphone and computer vision solutions have gained traction due to their potential use in home monitoring and telemedicine (Table 2.2).

Table 2.2 Summary of currently available technologies for digital assessment of bradykinesia in Parkinson's Disease

Technology	Advantages	Disadvantages	Use cases	References
Glove touch sensor (worn on two fingers or as a "data glove")	- Simple to use, familiar interface - Can measure fine motor movements	- Limited to one finger tapping task - Prone to calibration drift	Index and thumb tapping tests, hand movements	(Abbas et al., 2020; Bobić et al., 2019; Yokoe et al., 2009)
Gyroscopes	- Measure angular velocity, good for rotational movements	- Sensitive to noise, require calibration and correction	Wearable during daily activities, gait analysis, neurological assessment	(Memar et al., 2018; Mera et al., 2012; Salarian et al., 2007; Sigcha et al., 2022)
Accelerometers	- Measure linear acceleration, good for limb movement amplitude, dyskinesias	- Sensitive to gravity, require calibration for absolute position	Popular in passive monitoring, gait analysis, hand movements	(Griffiths et al., 2012; Mahadevan et al., 2020; Memar et al., 2018; Sigcha et al., 2022)
Magnetometers	- Measure magnetic field changes, can track limbs without direct contact	- Limited range, susceptible to metal interference	Wrist actigraphy, gesture recognition, body sensor systems	(di Biase et al., 2018)
Mechanomyography	- High accuracy for muscle contraction (takes account of rigidity)	- Expensive, limited range - Less validated than EMG	Motion capture systems, gait analysis	(Huo et al., 2020)

	- Non-invasive alternative to EMG			
Cameras/Computer Vision	- Non-invasive, can capture full-body movements	- Requires dedicated hardware, privacy concerns, complex algorithms	Video-based gait analysis, pose estimation	(Morinan et al., 2023)
Smartphones/Tablets	- Readily available, can utilize built-in sensors and cameras	- Lower accuracy compared to dedicated devices, limited battery life	Gait analysis using smartphone accelerometers, finger tapping on displayed targets	(C. Y. Lee et al., 2016; W. Lee et al., 2016; Printy et al., 2014)
Gait measurement techniques that could be potentially applied to bradykinesia				
Force sensor	Measures force exerted by shoes on a walking mat			(Bae and Tomizuka, 2013; Shah et al., 2018)
Electromyography	Registers electrical signals of motor unit activity in muscles. Can be used for walking performance and posture.			(Geroin et al., 2017; Rainoldi et al., 2004)
Goniometry	Measures flexion, good for study of angles for ankles, hips, knees, metatarsals. Can be integrated into shoes with other sensors.			(Bamberg et al., 2008)
Impulse radio ultra-wideband	Measures movements non-invasively by emitting and recording ultra short radio waves			(Yim et al., 2019)
Ultrasound sensors	Can be used to estimate distance between steps, detect gait phase and gait symmetry			(Wahab and Bakar, 2011)
Time of Flight (ToF)	ToF systems measure the phase-shift between the camera and the subject to estimate distances. Can be used to capture the segment position, gait phase, foot plantar pressure distribution.			(Samson et al., 2012; Tucker et al., 2015)

A single-finger sensor could offer potential advantages over complex set-ups through cost-effectiveness, simplicity, and portability. This technology has been explored in several studies. Dlamini et al. (2021) employed an accelerometer and gyroscope sensor worn on the index finger to assess individuals at increased environmental risk for PD. Machine learning algorithms trained on this data successfully automated MDS-UPDRS assessment in both manganese-exposed and non-exposed populations, suggesting potential for screening and community-based applications (Dlamini et al., 2021). Heldman et al. (2014) evaluated the same sensor in laboratory settings, comparing its performance to expert clinician ratings of upper body bradykinesia. Their findings revealed superior test-retest reliability and sensitivity to minimal detectable changes for each DBS amplitude (Heldman et al., 2014). The authors further explored this sensor's potential by demonstrating its feasibility in telemedicine applications

(Heldman et al., 2017a). Espay et al. (2011) investigated whether a single sensor data can be used to assess physiological response to medication. Their findings revealed that dopaminergic treatment differentially affects the speed, amplitude, and rhythm of upper body movements (Espay et al., 2011).

Similar observations were reported by Tamás et al., who found that sensor data aided in assessing the impact of STN-DBS therapy on upper body bradykinesia. These findings suggest that detailed analysis of movement components using sensor data can inform therapeutic adjustments, potentially improving patient outcomes. Isaacson et al. (2019) tested this concept in a real-world scenario. Their study investigated the impact of continuous motor symptom monitoring with the single-finger device on clinical decision-making in patients initiating rotigotine patch therapy. Compared to standard care, patients using the device experienced greater improvements in motor symptoms and received more frequent dosage adjustments, suggesting its potential to optimize treatment and improve patient outcomes (Isaacson et al., 2019). Whilst the results of these studies are encouraging, most have been conducted on small and cross-sectional populations. There are also outstanding questions on whether a single sensor can provide a signal of adequate quality to justify its use in routine automation of MDS-UPDRS assessment.

2.1.3 Objectives

The present study aims to establish whether a single-finger sensor can reliably measure the bradykinesia components of MDS-UPDRS examination in a large longitudinal study and produce results comparable to an MDS certified clinician.

2.2 Methods

2.2.1 Participants and protocol

Measurements obtained for all chapters of this thesis originate from the Oxford QUantification In Parkinsonism (OxQUIP) Phase 1 study. OxQUIP Phase 1 was a longitudinal investigation conducted at the John Radcliffe Hospital in Oxford, UK. The study's primary objective was to identify measures that effectively detect disease progression. This was

achieved by recruiting a large cohort of participants from diverse backgrounds and a wide range of disease severity. A unique feature of OxQUIP was the inclusion of several groups of patients with PD: *de-novo* (unmedicated), early (<8 years of diagnosis), advanced (>8 years), and those undergoing Deep Brain Stimulation (DBS) surgery. Participants with Progressive Supranuclear Palsy were also included. The control group was devised from age-matched, healthy volunteers who were recruited primarily, but not always, from spouses of the participants. This was done to minimise differences in environmental exposure. All participants were followed up every three months, for up to nine visits. The recruitment was initiated in November 2016 and continued recruiting until 2019. Unfortunately, due to COVID-19 pandemic, a few participants needed to complete the study prematurely.

A diagnosis of PD was made by a movement disorder neurologist, based on the MDS criteria (Postuma et al., 2015). Patients with any other neurological or psychiatric disorder were excluded. All subjects were in their ON medication state, except for the second visit when they were tested in both the OFF and ON states (levodopa challenge; OFF medication was defined as at least 12 hours after the previous dose of levodopa). Both upper limbs were included in the analysis. During every visit, participants were invited to attend an in-person research clinic at the John Radcliffe Hospital. The same battery of tasks was administered every time: clinical examination, wearable sensors assessment, finger-tapping, eye-tracking and cognitive measurements.

The OxQUIP study was approved by relevant ethical committees (REC 16/SW/0262All participants were given written information about the study, and informed consent was obtained prior to participating.

2.2.2 Human-based data collection

MDS-UPDRS assessment was conducted by MDS-trained and certified clinicians from the OxQUIP study. The following upper body bradykinesia metrics were analysed: finger tapping (item 3.4), hand movement (grasping) (item 3.5) and pronation supination (item 3.6). The participants were asked to achieve as large amplitude and as fast movement as possible over 15 seconds (Fig. 2.1 A, B). Scores were assigned as per MDS instructions with a range of 0 (asymptomatic) to 4 (unable to perform or barely performing the task). Only integer marks

were given. Additionally, commonly used disease severity and quality of life metrics were obtained through self-reports and clinical assessment. These were MDS-UPDRS Part 3 Total Motor Score, Hoehn and Yarh Stage (Hoehn and Yahr, 1967), and Schwab and England Activities of Daily Living Score (Schwab, R.S and England, A.C., 1969).

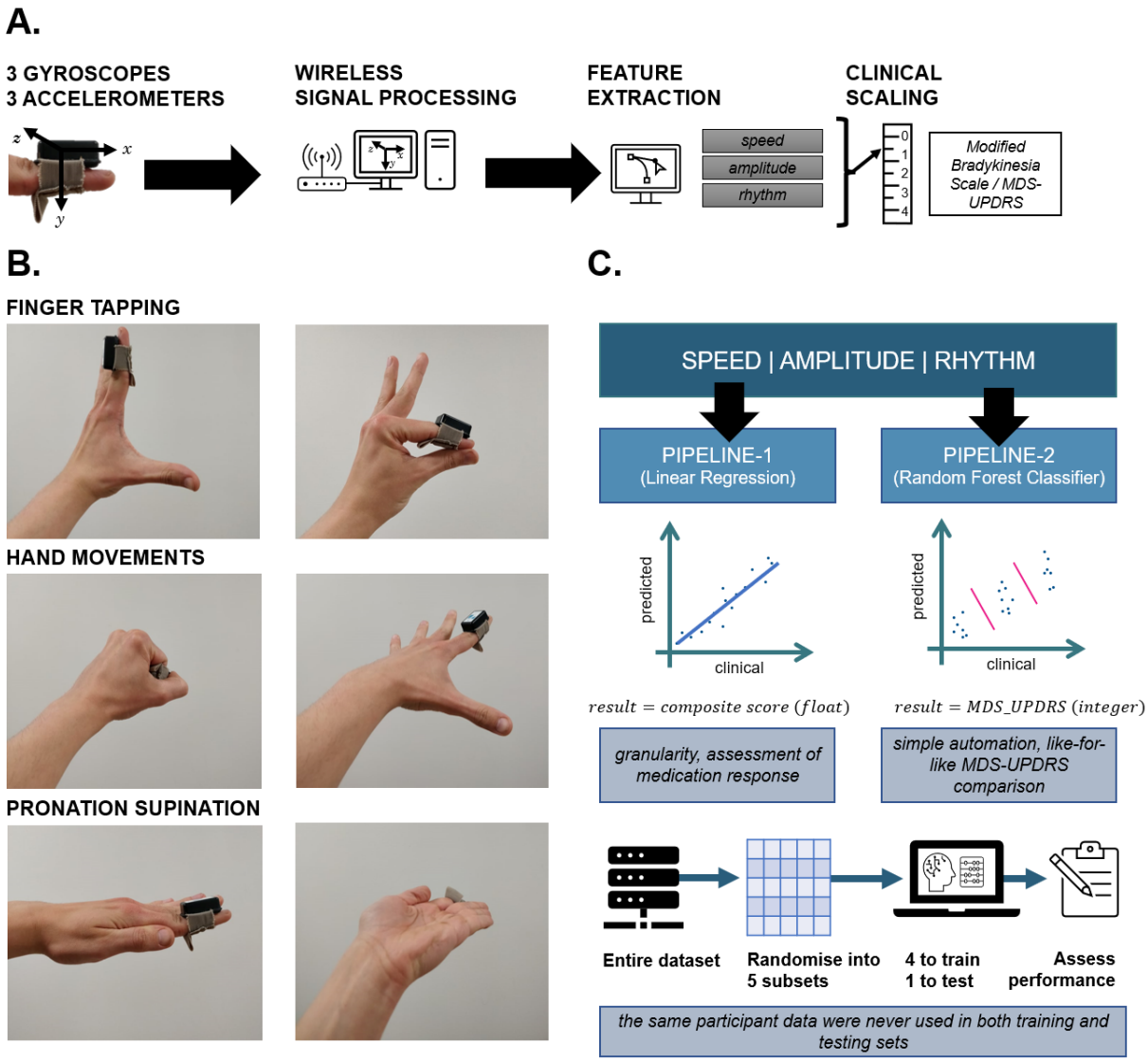


Figure 2.1 Summary of experimental methods. (A) Data processing: from raw gyroscopic and accelerometer signal acquisition to scaling the data against clinical scores. (B) Photographs of three tasks in the bradykinesia subset: repetitive finger tapping with thumb and index finger, hand movements of making a fist and extending fingers, pronation supination of a flat hand. (C) Two presented pipelines for a granular digital MDS-UPDRS (linear regression) and automated digital MDS-UPDRS - (ordinal regression). Validation methods for a five-fold split of the dataset. MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale.

2.2.3 Sensor-based data collection

Participants wore a wireless sensor comprising three orthogonal accelerometers measuring linear acceleration and three orthogonal gyroscopes measuring orientation and angular velocity in three dimensions at a sampling frequency of 128Hz (Kinesia system, Great Lakes Neurotechnologies, Inc., Cleveland, OH). This was worn while the standard clinical examination took place (Fig. 2.1 A-C). The data were wirelessly transmitted through a tablet to the manufacturer's online platform where it was processed, using their proprietary algorithm (Giuffrida et al., 2009). Within the Kinesia processing software, the signal was bandpass filtered from 0.3-5Hz using a second-order Butterworth filter. To minimise errors resulting from slight variations in the orientation of sensors on the finger and thumb, the magnitudes (Euclidean norm) of the angular velocities around the x-, y-, and z-axes were calculated. Speed was calculated as root-mean-square of angular velocity, amplitude as root-mean-square of excursion angle, and rhythm as coefficient of variation of excursion angle. These values were then scaled according to the movement neurologist's assessment of these components in the modified Bradykinesia scale: 0 to 4 for speed, amplitude, and rhythm for each of the tasks (finger tapping, hand movement, pronation supination). The standardisation was conducted by blinded and randomised assessment of video recordings from an already published training set (Giuffrida et al., 2009). The format of the resulting output is a float number for speed, amplitude, and rhythm for each of the measured items in the range 0-4. This algorithm is a widely used method of digital bradykinesia assessment and has been approved and recommended by the National Institute of Health and Care Excellence (NICE) guidelines for monitoring of PD symptoms (diagnostics guidance [DG51]) (NICE, 2024). Therefore, to achieve direct comparability of this study with the previously published data, no changes were made to the data extraction analytical pipeline.

2.2.4 Extraction of sensor-based outcomes

Wearable sensor-based metrics were derived using two data analysis pipelines, based on linear and ordinal regression algorithms. A linear regression-based model was constructed to calculate a composite digital (predicted) MDS-UPDRS score.

This was done so that:

$$\text{digital MDS-UPDRS} = \beta + x * \text{speed} + y * \text{amplitude} + z * \text{rhythm}$$

where factors β, x, y and z were coefficients optimised to minimise the root mean squared error (RMSE) of the sensor-derived MDS-UPDRS, using clinically assessed MDS-UPDRS as target variable. The linear regression model was chosen to create a continuous digital MDS-UPDRS score and assess relative contributions of individual components (speed, amplitude and rhythm) to the final estimation. While the clinically administered MDS-UPDRS utilises a discrete ordinal scale (0-4) for practical reasons of simplification standardisation, the underlying physiological phenomenon of bradykinesia exists on a continuous spectrum. Therefore, a continuous digital MDS-UPDRS score more closely reflects the true physiological state of the patient. However, fitting granular digital data against a categorial MDS-UPDRS variable will inevitably result in large RMSEs in a linear regression model. Whilst this could be acceptable in the estimation of the "true" continuous MDS-UPDRS, there are situations where a direct, like-for-like comparison between digital and human-assessed UPDRS is desirable. To achieve this, a random forest (ordinal target) model was utilised, which fitted the three components (speed, amplitude, rhythm) against a categorical (0 to 4) variable, resulting in an integer score.

2.2.5 Model evaluation

To avoid overfitting, five-fold cross-validation was performed in both pipelines, making sure that the split was made by randomising individual participants, and that no participant data appeared in both training and testing sets. RMSEs and coefficients were averaged across these five tests and final values were reported. Intraclass correlation coefficient (ICC) was calculated to assess the agreement between linear regression model estimation and clinical ratings. ICC specifically quantifies the consistency and concordance between two measurement methods, accounting for both within- and between-method variability, unlike simpler correlation measures that only assess linear relationships. Since the study focused on evaluating the consistency of the sensor-based measurements with the clinical ratings, rather than

requiring perfect absolute agreement between the two methods, a relative as opposed to direct ICC method was used. Cohen's Kappa was used to evaluate the accuracy of the predictions made by ordinal regression. This metric evaluates the agreement between the categorical digital MDS-UPDRS scores (generated by the ordinal regression model) and the clinically assigned MDS-UPDRS ratings, as both are ordinal measures. Individual MDS-UPDRS items data were not normally distributed, with values skewed toward the left (healthier) side. This resulted in class imbalance, which could bias machine learning models, leading them to perform well on the majority class (healthier) but poorly on the minority class (more severe), which is often of greater clinical interest. This was corrected using by Synthetic Minority Oversampling Technique (SMOTE) which creates synthetic samples of the minority class to balance the dataset, thus improving the model's ability to accurately predict all levels of bradykinesia severity. To avoid data leakage, the SMOTE rebalancing was performed within each fold as opposed to before inputting the data into the model (Chawla et al., 2002; Imbalanced, 2023). For the assessment of levodopa challenge, the F-test was used to compare the variability (specifically, the variance) of the change in MDS-UPDRS scores between the digitally predicted scores and the clinically assessed scores. Since administration of levodopa was a well-recorded, independent variable, lower metrics of variance should indicate a more reliable method of assessment.

2.3 Results

2.3.1 Patient population

This chapter focuses on sixty-eight participants with early (<8 years) diagnosis of PD. A summary of demographics is provided in Table 2.3. Their mean baseline MDS-UPDRS Part III (motor) score was 17.5 points (range 0-52). Three participants (4.4%) reported dyskinesias and motor fluctuations, however none interfered with the MDS-UPDRS ratings (as per last item of the scoring sheet). The mean Schwab & England activities of daily living scale was 91.5 points (range 70-100).

Table 2.3 Summary of demographic data for the studied sample

Parameter median	Median (Inter Quartile Range)
N	68
Age (IQR)	65 (11)
Sex (Male/Female)	39/29
Months since diagnosis (IQR)	30 (30)
Side of Symptom onset (Right/Left)	26/41
Dominant side (Right/Left/Ambidextrous)	61/5/1
Montreal Cognitive Assessment Score (MoCA) (IQR)	27 (3.5)

A total of 6240 observations were collected from 520 unique clinical visits. Each observation consisted of a sensor or clinical assessment reading of a given limb (left or right): one MDS-UPDRS item score or one corresponding set of three sensor subcomponent scores for that item. The MDS-UPDRS measurements were conducted by six independent and randomly allocated MDS certified clinicians. A notable but expected skewness towards the healthier side was observed (skewness: 0.64, 1.11, 0.88 for finger tapping, hand movement and pronation supination respectively).

2.3.2 Model performance – Linear Regression

The bradykinesia scores (MDS-UPDRS items 3.4-3.6) obtained from the clinician and the linear regression model had a highly significant good to moderate agreement, with intraclass correlation ranging 0.76 to 0.68 (Table 2.4). The distribution of residuals of the sum of MDS-UPDRS bradykinesia items had a mean of 1.0, which indicates that overall, the linear regression model tended to slightly overestimate MDS-UPDRS ratings. Large disagreements constituted a small proportion of the sample. For 95.6% of assessments, the disagreement between the clinician ratings and model estimations fell below the large Clinically Important Difference (CID) threshold of 3.6 MDS-UPDRS points (Shulman et al., 2010). It emerged that individual MDS-UPDRS item subcomponents (speed, amplitude, and rhythm) contributed in different strengths to the final model estimator. For finger tapping, the coefficients were: 0.62, 0.34, and 0.15, (RMSE 0.76) (Fig. 2.2A). In the hand movement task, speed was the dominant contributor again (0.53) with amplitude and rhythm coefficients of 0.30 and 0.29 respectively (RMSE 0.73). In the pronation supination task, the amplitude was the dominant feature,

contributing to half the score (0.50). The coefficient for speed was 0.36, with rhythm contributing the least (0.20) (RMSE 0.84).

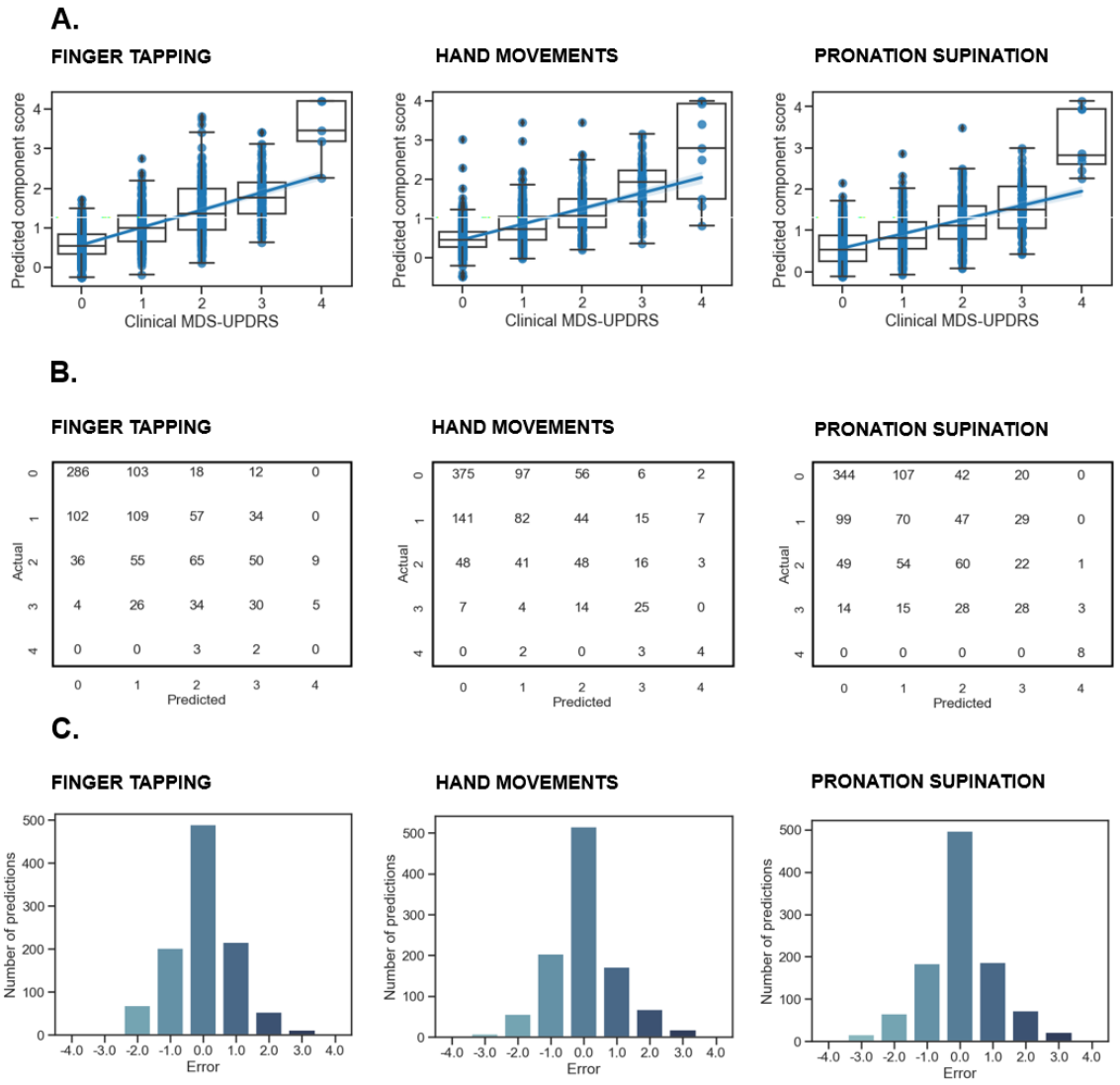


Figure 2.2 Summary of the results from both pipelines. (A) Linear regression fit of digitally predicted vs clinical MDS-UPDRS component scores (B) Confusion matrices showing matching between predicted and clinical MDS-UPDRS component scores from ordinal regression model (C) Difference between predicted and clinical MDS-UPDRS component scores from ordinal regression model. Error of 0 indicates perfectly predicted scores for a given MDS-UPDRS component. The box plots show interquartile ranges, the median is indicated by the centre line, the whiskers indicate 2nd and 98th percentiles, circles are the outliers.

Table 2.4 Summary of agreement statistics between clinical MDS-UPDRS scores and linear regression model estimates.

Feature	Clinical score	Model estimates	Agreement			
	Mean (SEM)	Mean (SEM)	n	ICC	95% CI	p
Finger tapping	1.01 (0.03)	1.01 (0.02)	2080	0.76	[0.73, 0.78]	5.92×10^{-7}
Hand movement	0.76 (0.03)	0.75 (0.02)	2080	0.72	[0.69, 0.76]	3.0×10^{-9}
Pronation supination	0.88 (0.03)	0.87 (0.02)	2080	0.68	[0.63, 0.71]	1.52×10^{-7}

ICC = Intraclass correlation coefficient, SEM=Standard error of the mean.

2.3.3 Model performance - Ordinal regression

The accuracy of the ordinal regression was assessed by Cohen's Kappa. This statistical method assesses overall performance of the model to classify three input features (speed, amplitude, and rhythm) into an integer score of MDS-UPDRS item. The coefficients were: 0.25, 0.23, and 0.23 for finger tapping, hand movement, and pronation supination MDS-UPDRS items respectively (Fig. 2.2B). The model achieved an overall accuracy of 85.2% correctly classified observations within 1 MDS-UPDRS point (Fig. 2.2C). The relative feature importances of speed, accuracy and rhythm were similar for all three tasks: finger tapping 0.35, 0.35, 0.3; hand movement 0.33, 0.33, 0.34; pronation supination 0.34, 0.34, 0.32.

2.3.4 Clinical relevance - Levodopa challenge

Using the linear regression coefficients for the bradykinesia tasks, a model predicted bradykinesia score was calculated. Differences in clinically assessed and digitally predicted MDS-UPDRS were compared between OFF and subsequent ON state, during their second visit. The digital measurement was able to assess this change with less variability (F test $p<0.001$); mean -2.02 points 95% CI [-2.21, -1.82] vs clinically assessed mean change of -1.22 points 95% CI [-1.55, -0.89] (Fig. 2.3). Clinically assessed MDS-UPDRS assessment was also more prone to errors, whereby clinicians incorrectly assigned a worsening score after the introduction of medication.

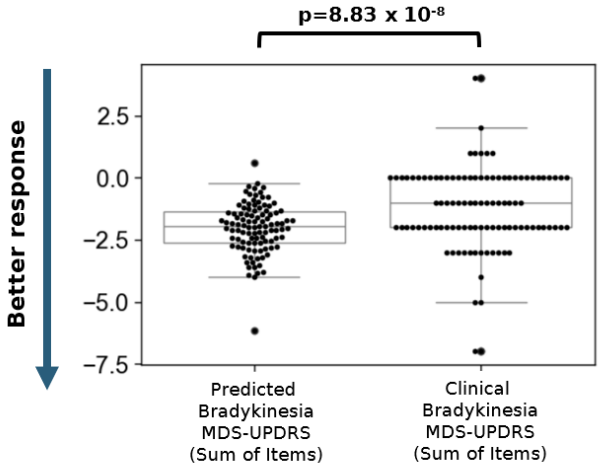


Figure 2.3 Response to levodopa challenge (change in sum of bradykinesia MDS-UPDRS component scores when levodopa is re-introduced after >12 hours). Individual responses of participants when assessed by digitally predicted and clinically assessed MDS-UPDRS. A negative score indicates improvement. P value relates to F test for difference in variances. The box plots show interquartile ranges, the median is indicated by the centre line, the whiskers indicate 2nd and 98th percentiles, circles are the outliers.

2.4 Discussion

2.4.1 Automating MDS-UPDRS assessment in PD

A single-finger sensor was used to measure finger tapping, hand movements, and pronation-supination in PD patients. Using automated analysis pipelines, scores from clinically assessed MDS-UPDRS were estimated through machine learning models. The ordinal regression model achieved an accuracy comparable to an MDS-certified clinician assessment, with 87.5% of results falling within a margin of error of 1 MDS-UPDRS point. The linear regression model estimations proved to exhibit a high agreement (mean ICC 0.72, $p<0.0001$) with the expert MDS-UPDRS assessments. Large disagreements constituted a small proportion of the sample. For 95.6% of assessments, clinician and model disagreements fell below the CID threshold, meaning that estimation errors made by the models were unlikely to have major clinical significance. Sensor-based measurements also showed a lower degree of variability when assessing response to reintroduction of medication during levodopa challenge. This could be at least partly due to the added precision provided by the float number format, compared to the categorical clinical scale. The model proved most reliable in estimating mild to moderate disease (MDS-UPDRS score of 1-3). This was an expected result given that MDS-UPDRS

clinical rating of 0 can only be matched or overestimated by the model. This resulted in a trend towards an overestimation in the model-estimated composite score. Higher severity scores are also more difficult to estimate due to outpatient recruitment and the ceiling effect of the maximum score.

Motor dysfunctions in PD can be highly variable between patients and may differentially affect several aspects of movement (Greenland et al., 2019; Myers et al., 2021; Shakya et al., 2022). This was investigated in our work by showing coefficients for speed, amplitude, and rhythm. We demonstrated that they contribute unequally to the final score for the task. This can be a desirable additional information for clinicians, as medication or surgical interventions may only affect one aspect of bradykinesia. Changes in antiparkinsonian medication preferentially improve speed, whereas DBS has a greater effect on amplitude (Kim et al., 2013). Transcranial alternating current stimulation (tACS) on the primary motor cortex worsens movement velocity in β-tACS setting and improves movement amplitude with γ-tACS (Guerra et al., 2022). These discrete signals may be obfuscated when individual subcomponents are not presented. Many clinical studies simply report the total MDS-UPDRS Part 3 motor score, in which such a subtle change will invariably be lost to statistical insignificance. This detailed information could be used by clinicians to improve decision making and understanding of the complexities of motor impairments in PD.

In summary, the results of this study corroborate previous findings that wearable gyroscope and accelerometer sensors can replicate MDS-UPDRS scores with similar agreeability across the literature (Chan et al., 2019; Hadley et al., 2021; Heldman et al., 2016a; Jia et al., 2014; Pulliam et al., 2018). They can provide a precise estimation of medication response in PD (Espay et al., 2011; Heldman et al., 2017a), and also measure effects of deep brain stimulation (Heldman et al., 2016b; Mera et al., 2011, 2013; Sasaki et al., 2021). The ICCs show an acceptable agreement with the human experts and are similar to those obtained from computer vision studies (Hong et al., 2024; Morinan et al., 2023). The overall accuracy of MDS-UPDRS approximation is comparable to smartphone software packages like CloudUPDRS (Jha et al., 2020) or Roche PD (Lipsmeier et al., 2018). This contributes to the body of evidence that digital PD assessment models could be used as complementary tool for clinical trials and routine movement disorder practice.

2.4.2 Levodopa challenge

A major advantage of the linear regression model was its ability to measure the response to a levodopa challenge. Patients are expected to improve their scores after administration of medication, although the extent of response can vary (Kempster et al., 2007). The linear regression model was able to encapsulate this diverse range of responses with a more granular and less noisy metric. This was evidenced by lower variance in the linear regression model vs clinically assessed MDS-UPDRS. This level of granularity could prove advantageous in clinical trials, where a more precise threshold for "clinically meaningful change" can be set to evaluate new drug candidates, especially in an outpatient setting (Cubo et al., 2017; Hadley et al., 2021; Heldman et al., 2016a; Hoffman and McNames, 2011; Mera et al., 2012; Pulliam et al., 2018).

The limitations of levodopa challenge should also be discussed. In some cases, clinical scale values were worse in the "ON" state, which is not physiologically expected (Saranza and Lang, 2021). This was likely due to an imprecision of measurement rather than a genuine decline, although the effects of fatigue cannot be excluded. It is important to note that in our study, raters had no direct access to "OFF" state scores when assessing the "ON" state, and thus it is reasonable to assume that a small difference could be attributed to inter-rater variability. It is conventionally accepted that any reaction lower than 30% on the total MDS-UPDRS Part 3 Motor score is unlikely to be clinically significant (Hong et al., 2024; Merello et al., 2011; Saranza and Lang, 2021). Possible methods of circumventing this limitation include administration of additional (150-200%) dose of dopamine to amplify the medication reaction signal (Langston et al., 1992), although this would be impractical in this study and is not commonly used. Washout periods could also be extended. In ELLDOPA study a washout period of two weeks was used for the "OFF" state assessment, and even longer, 32-day levodopa deprivation (four half-lives) was suggested (The Parkinson Study Group, 2004). It is also difficult to standardise the time to "ON" state, as most participants will be at various points between their full "OFF" and "ON" state during a single clinic (Hauser and Holford, 2002). Poor drug absorption may also contribute to the "negative" levodopa challenge (Ogawa, 2000). Regardless of the various definitions of levodopa unresponsiveness, these data taken together show the advantage of using a more stable and granular metric like sensor-derived estimations.

2.4.3 Limitations and future directions

While the results of this chapter provide valuable insights, certain limitations should also be acknowledged. The linear regression model featured relatively large RMSEs. This could be for several possible reasons. First, the model based on linear regression attempts to fit a continuous digital MDS-UPDRS against a categorical human MDS-UPDRS, which results in unavoidable differences between integer and float numbers. Second, the MDS-UPDRS does not allow decimal points and is thus reliant on clinicians rounding their scores to the nearest whole number. There is no universally accepted way of performing this approximation, and it is likely that a large degree of variability is exercised by clinicians in this regard. Only subjective descriptions are provided, e.g. severity of 1 indicates “slight slowing”, 2 “mild slowing”, etc. Such imprecision in instructions could explain some rater disagreements. The MDS-UPDRS instructions mandate compression of speed, amplitude, and rhythm assessments into a single feature. The final subcomponent score is decided based on the worst of the three, which results in the score defaulting to the highest digit, regardless of their relative imbalance.

Due to the inherent variability of clinical assessments, perfect agreement between a model and a single clinician's rating is neither expected nor desirable. Such complete alignment could actually suggest overfitting to individual biases. Instead, our machine learning models were tasked to emulate a weighted average of expert judgments. This approach, aligned with the "wisdom of crowds" principle, has the potential to limit the influence of individual human error on the overall assessment. Another way of attenuating these imprecisions would be to introduce multiple raters, e.g. through double-marking of the video-recorded tasks (Heldman et al., 2014). The OxQUIP study was designed to test participants alongside their routine clinical care and thus no video recordings were available. It was impractical to have more than one rater per participant, per visit in an in-person clinic. We attempted to avoid “over-fitting” to a single opinion or individual bias by using a large and heterogeneous dataset (over 6000 ratings) and by randomly allocating raters, such that the same participant may be seen by different raters, at different stage of their disease within the two-year follow up.

While this study demonstrates promising results in automating MDS-UPDRS assessment using a single-finger sensor, a key limitation is the absence of external validation data. The models were trained and tested on data from the same cohort, which may limit their

generalizability to other populations or clinical settings. Future work should prioritize validating these findings with independent datasets to confirm their robustness and clinical utility.

2.4.4 How were patients involved in the study?

Patients trialling the single finger sensor noted its ease of use and seamless integration. Some participants expressed concerns about a potential risk of sensor misplacement due to its small size and dark colours. This was raised as especially important if the sensor were to be used for home monitoring. The OxQUIP Patient and Public Involvement (PPI) group highlighted the benefits of automated, remote neurological assessment in overcoming logistical difficulties like hospital parking and travel, thus offering a convenient alternative for those facing access barriers. They suggested this solution could be used as part of a telemedicine clinic with their neurologist.

2.5 Conclusions

Single-finger sensor kinematic data coupled with machine learning models offers a reliable and objective tool for automated bradykinesia assessment in PD. There was a high agreement between digital metrics and expert MDS-UPDRS scores across visits, particularly in mild-to-moderate disease. The model further revealed the differential contributions of speed, amplitude, and rhythm to overall bradykinesia assessment. Sensor data also effectively tracked levodopa response, providing a fine-grained evaluation of physiological changes. We propose this methodology as a complementary tool for automating PD bradykinesia assessment, potentially improving objectivity and granularity.

3

Kinematic Data Track Masking of Motor Symptoms After Introduction of Antiparkinsonian Medication

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DOI: 10.1016/j.heliyon.2023.e16415.

3.1 Introduction

3.1.1 Endogenous synthesis and transport of dopamine

Dopamine (DA) is an endogenous catecholamine that plays a key role in the central nervous system (CNS). It modulates various physiological functions in brain areas involved in voluntary movement, reward processes, and cognitive functions such as attention, learning, and memory (Bernardi and Mercuri, 2009). DA molecules are synthesised within dopaminergic neurons (Neve, 2010). Although pure DA can be ingested, it does not cross the blood-brain barrier (BBB). Neural signalling is therefore conducted either through endogenous synthesis or exogenous provision of precursors or enzyme agonists. The direct precursor of dopamine – levodopa – can be synthesised either directly from the non-essential amino acid tyrosine or indirectly from the essential amino acid phenylalanine (Musacchio, 1975). These amino acids are ubiquitous in most diets. L-Phenylalanine is converted into L-Tyrosine by liver phenylalanine hydroxylase. L-Tyrosine then crosses the BBB via active transport and is converted into levodopa by tyrosine hydroxylase. Levodopa is then converted into DA by DOPA decarboxylase enzyme (DDC, also known as Aromatic L-amino acid decarboxylase,

AAAD). This forms the primary pathway of CNS dopamine conversion. There is also a second, "minor" pathway, in which L-Tyrosine is converted to P-Tyramine by DCC. P-Tyramine is then converted to DA using CYP2D6 cytochrome (Musacchio, 1975).

DA acts as a neurotransmitter and neuromodulator by binding to and activating cell surface receptors. Five subtypes of dopamine receptors have been found in humans. All are G protein-coupled type receptors. These five subtypes (D1 to D5) are usually grouped into two families – D1-like and D2-like. D1 receptors increase intracellular levels of cAMP by activating adenylate cyclase, stimulating the downward signalling pathway via the opening of the sodium channels. Conversely, D2-like receptors decrease cAMP and lower the rate of adenylate cyclase function, which exerts an inhibitory effect via the opening of the potassium channels (Romanelli et al., 2010).

Once synthesised, DA is transported from cytosol to synaptic vessels of a neuron by vesicular monoamine transporter 2 (VMAT2). DA is stored in these vessels until ejection to the synaptic cleft, which occurs upon stimulation from action potential or increased activity of the trace amine-associated receptor. In the synapse, DA binds to D1- or D2-like postsynaptic receptors or presynaptic autoreceptors (e.g. autoinhibitory D2-sh or D3 receptors). After the post-synaptic neuron elicits the action potential, DA molecules become rapidly unbound from receptors. A process of reabsorption and degradation begins. Reuptake of DA is facilitated by dopamine transporter (DAT) or plasma membrane monoamine transporter (PMAT). Once back in the cytosol, DA can be reused and repackaged into VMAT2 vesicles. The remainder is degraded by monoamine oxidase into 3,4-Dihydroxyphenylacetic acid (DOPAC) and excreted for further conversion to homovanilic acid by Catechol-O-methyl transferase (COMT) enzyme (Eiden et al., 2004; Masato et al., 2019). Two mechanisms modulate this process – phasic and tonic transmission. Phasic DA release is the most common system, driven directly by presynaptic action potentials. Tonic transmission occurs without the action potential and involves a release of small amounts of DA. It is regulated by neighbouring neurones and DA reuptake (Rice et al., 2011). These pathways play a crucial role in dopamine deficiency physiology and have served as drug targets for several PD treatment options (Fig. 3.1).

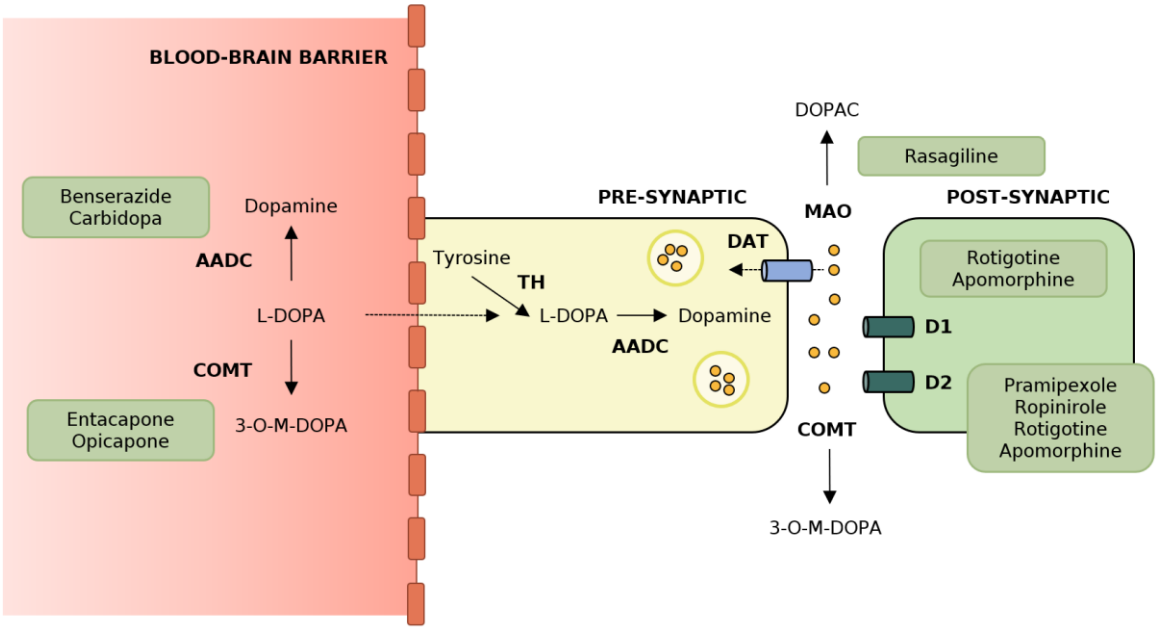


Figure 3.1 Summary of pre and postsynaptic dopamine metabolism with selected drug targets in green boxes. Enzymes are shown in bold: AADC = Aromatic amino acid decarboxylase, COMT = Catechol-O-methyltransferase, MAO = Monoamine oxidase, TH = tyrosine hydroxylase. L-DOPA = Levodopa, DAT = dopamine transporter, D1, D2 are dopamine receptors. Figure on the basis of review (Poewe et al., 2017).

3.1.2 Exogenous dopamine administration

Administration of levodopa has a long history in the treatment of PD. It was first used in ancient Indian and Chinese medicine, where dopa-rich *Mucuna pruriens* beans were used to relieve symptoms of "paralysis agitans" (Fahn, 2008; Manyam, 1990). The scientific basis of levodopa supplementation use was later established in the 1950s and 60s. A series of experiments by Swedish scientist Arvid Carlsson demonstrated the key role of DA in CNS motor control, suggesting that a restoration of DA in basal ganglia could reverse akinesia and reduce tremor. This discovery subsequently earned him a Nobel Prize in Medicine or Physiology (Horowski and Löschmann, 2019). Levodopa was initially delivered intravenously, which proved challenging due to severe neurotoxicity. George Cotzias, a Greek scientist, and neurologist at Harvard and Massachusetts General, suggested an oral route, with a very small dose given over two hours. In 1968, he conducted a landmark study, which demonstrated a remission of PD symptoms when stable dosing of levodopa was achieved (Cotzias, 1968). Since then, many new methods of improving drug dosing, absorption and administration have been developed, offering a wide variety of treatment options available to movement disorder physicians (LeWitt, 2016).

In the early years, PD patients have relatively preserved substantia nigra function. This means that levodopa can effectively alleviate their symptoms, even beyond the 90-minute half-life (Zhang et al., 2022). As the disease progresses, nigrostriatal degeneration reduces the therapeutic window of each dose, leading to the "wearing-off" effect, characterized by worsening symptoms prior to the next dose (Paolini Paoletti et al., 2020). While increasing dosage frequency temporarily alleviates this issue, further disease progression exacerbates therapeutic window narrowing and renders motor complications increasingly unpredictable (Carrarini et al., 2019; Hong et al., 2020). These complications stem from disease severity, changes in the gastrointestinal tract and accumulated levodopa use (Freitas et al., 2016). Advanced PD patients frequently experience fluctuations between akinetic states (excessively low levodopa) and dyskinetic states (excessively high levodopa) (Stocchi et al., 2008). Dyskinesias are characterised by involuntary, hyperkinetic movements of the limbs, trunk, neck, and face, whilst akinesias manifest as increased hesitations, freezes and rigidity (Amato et al., 2018). These phenomena arise from pre- and post-synaptic dopamine fluctuations within the nigrostriatal pathway, and can cause severe distress and quality of life impairment (Nonnekes et al., 2016).

To minimize the side effects of DA level fluctuations (e.g. dyskinesias, hyperrigidity), combinations such as carbidopa-levodopa (co-careldopa) and benserazide-levodopa (co-benaldopa) are frequently prescribed. These paired medications include L3,4-dihydroxyphenylalanine (DOPA) decarboxylase inhibitors, benserazide and carbidopa. Because these inhibitors are polar and unable to cross the blood-brain barrier (BBB), they selectively prevent peripheral levodopa-to-DA conversion, allowing levodopa to reach the brain intact (Beckers et al., 2022). Co-prescription with COMT inhibitors such as entacapone and opicapone reduce peripheral degradation of DA to 3-O-M-DOPA, which improves DA availability in peripheral blood (Rivest et al., 1999). MAO-B inhibitors (rasagiline, selegiline) prevent central DA breakdown and depletion (Tan et al., 2022), which means that these agents can be used as monotherapy in early PD or as an adjunct to complex levodopa formulation in more advanced disease. Technology-driven solutions can also improve plasma level fluctuations. These include intestinal gels and infusions, sustained-release micro tablets, gastric-retentive formulations, inhalations, subcutaneous infusions (LeWitt, 2016; Poewe and Antonini, 2015). These formulations have unique safety and efficacy profiles, and their availability has increased treatment options for PD patients (Navaratnam et al., 2022).

3.1.3 Dopamine agonists

Initially developed as adjunctive therapy to levodopa, dopamine agonists are now increasingly used as the initial monotherapy for young PD patients. This shift aims to postpone the need for levodopa and potentially delay the onset of extrapyramidal side effects (Stathis et al., 2015). Traditionally, two types of dopamine agonists were used in PD: ergot and non-ergot alkaloids (Cacabelos, 2017). Ergot derivatives, such as bromocriptine, cabergoline, lisuride, and pergolide, are now rarely used in PD due to potential risks of valvular heart disease and lung fibrosis (BNF (British National Formulary), 2024). Newer non-ergot agonists, such as pramipexole, ropinirole, rotigotine, apomorphine, and piribedil, are preferred options (Choi and Horner, 2024). Transdermal rotigotine patches offer a convenient option for patients with adherence issues (Reynolds et al., 2005). Apomorphine injections and subcutaneous infusions can be used in cases of severe motor fluctuations and sudden "off" episodes, where optimised oral and transdermal therapy have not been successful (Katzenschlager et al., 2018). Currently approved dopamine agonists primarily target D2/D3 dopamine receptors, with rotigotine and apomorphine exhibiting some D1 affinity (Isaacson et al., 2023). Selective activation of D1/D5 receptors has also been explored as a potential treatment avenue. Such agents, e.g. tavapadon (PF-06649751) and PF-06412562 (PF-2562), provide improvements in motor function, alertness and engagement in later disease, as demonstrated in early clinical trials (Lewis et al., 2023). However, challenges with pharmacokinetics, bioavailability, and adverse effects have so far limited their clinical advancement (Huang et al., 2020).

3.1.4 Physiology of first dopamine administration

Early and liberal use of levodopa is almost universally advocated in clinical guidelines (Fox et al., 2018; NICE, 2022). This means that the observation of the "true" unmedicated progression of PD has been difficult. The limitations of the studies in the pre-levodopa era and the hesitancy to withhold starting antiparkinsonian medication in clinical trials make this phenomenon particularly challenging to measure (Olanow, 2015). Studies across non-human primates, rats, and rabbits suggest that initiating pharmacotherapy leads to irreversible molecular and physiological consequences (De Deurwaerdère et al., 2017; Hershey et al., 2003; Lipski et al., 2011; Olanow, 2015). Differences in enzymatic activity have been observed within the substantia nigra and globus pallidus, affecting glutamic acid decarboxylase (Lloyd and Hornykiewicz, 1973), phospholipid metabolism (Riekkinen et al., 1975) and FosB

immunoreactivity (Cenci et al., 1999). Additionally, altered neurogenesis in subventricular zones (O'Keeffe et al., 2009), RNA damage in cortical and striatal areas (Svenningsson et al., 2000), and oxidative DNA disruption (Alam et al., 1997) have been observed. Levodopa metabolism can also generate toxic reagents like hydroxyl free radicals (Olanow, 1990) and semiquinones, known to damage the DNA, proteins and lipids (Olanow, 2015). Finally, disrupted serotonin metabolism in macaques and rats has been observed, with the development of dyskinesias at peak levels of exogenous DA provision (Carta et al., 2007; Riahi et al., 2012).

In humans, post-mortem studies corroborated some of the phenomena seen in animal models. Increased oxidation products can be observed in substantia nigra (Olanow, 2015), with the increase of dopamine concentration in the putamen and striatum (Lloyd and Hornykiewicz, 1970). Levodopa administration also attenuated striatal dopaminergic transmission in cortico-striatal connections (motor cortex, nucleus accumbens, frontal cortex), dispersed serotonergic pathways, and glial cells (De Deurwaerdère et al., 2017). Acute levodopa responses differ markedly between medication-naïve and treated PD patients. Brain imaging studies reveal distinct activation patterns in sensorimotor and ventrolateral prefrontal cortices, correlating with clinically observed changes in disease scores between these groups (Hershey et al., 2003). Notably, the initial levodopa intake can lead to a significant score improvement of around 40% (Cilia et al., 2020). Subsequent adjustments induce non-linear neuroplastic changes (Monte-Silva et al., 2010), modulated by individual patient sensitivity to levodopa (Herz et al., 2014). These observations highlight the uniqueness of initiating levodopa therapy, representing a non-replicable physiological event distinct from acute deprivation or high-dose stimulation. It is important to note that, despite theoretical concerns at the pre-clinical level, L-dopa does not appear to be directly toxic to the human brain (Lipski et al., 2011).

3.1.5 Characteristics of de novo PD patient populations

Newly diagnosed, unmedicated (often referred to as "de novo") 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. 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 of literature see Table 3.1). 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) (Marras et al., 2011; van den Heuvel et al., 2021). 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 (FitzGerald et al., 2018). Wearable movement sensors and digital forms of assessment are becoming increasingly popular in the study of neurodegenerative diseases (Brzezicki et al., 2021; FitzGerald et al., 2018) because of their precision and objectivity, and have been shown to discriminate between healthy adults and PD patients of different disease severity (De Vos et al., 2020a; Ricci et al., 2020a). 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. Although the use of wearable inertial sensors can identify medication-induced flattening of progression of motor features in de novo PD, little is known about the effect of levodopa on the longitudinal progression of measurements made using such systems.

Table 3.1 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., 2020b)	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)	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)	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)	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)	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)	24 de novo PD / 27 HC	Tested before and 1 hr 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., 2022)	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)	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)	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., 2012a)	13 de novo PD / 12 HC	After 3, 6 and 12 months	Wearable sensors	2-minute postural balance test	Slight decrease in sway dispersion and velocity compared to an increase in untreated
(van den Heuvel et al., 2021)	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

3.1.6 Objectives

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 signal. The hypothesis is that progression signals observed in the unmedicated state would be attenuated or even masked once symptomatic medication was started.

3.2 Methods

3.2.1 Participant selection

The data were derived from the unmedicated (de novo) arm of the OxQUIP study, which recruited 18 participants. To be eligible for inclusion in this analysis, participants needed to complete at least 2 visits before and 2 visits after starting their dopaminergic medication. Seven participants met these criteria, and their demographic data are presented in Table 3.2.

Table 3.2 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)

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. Upper limb bradykinesia was measured using a single inertial sensor (Kinesia^{TM} One, Great Lakes Neurotechnologies, Inc., Cleveland, OH), which captured the motion of the index finger. This was collected during MDS-UPDRS finger tapping, hand movement, and pronation supination tasks. Gait analysis was performed using six IMU sensors (Opal^{TM}, APDM, Portland, Oregon, USA). IMUs were worn by the participants on the sternum, lumbar region, and left and right wrists/feet during a two-minute straight level surface walk. Both sensors collected data at a sampling frequency of 128Hz. These devices were wirelessly connected to

the APDM MobilityLab System (MobilityLab^{TM}, APDM) for the extraction of standard, manufacturer-specified motor features related to the walk and sway tasks.

Participants 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. For each participant we defined visit 0 as the last study visit before the 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. Antiparkinsonian medication started before visit 1 is listed in Table 3.3.

Table 3.3 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

3.2.2 Sensor based data processing

The wearable sensors measured a large number of variables (>160 features – these will be discussed in more detail in Chapter 4). In order to reduce the dimensionality of the dataset, a feature selection protocol was applied (Fig. 3.2). Where the feature possessed left/right components, only features derived from the participant's most affected side were analysed. Features not relating to the testing protocol (asymmetry, anticipatory postural adjustments, and sway) were removed. We then analysed 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 a 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 the onset of medication (i.e. visit 1 onwards).

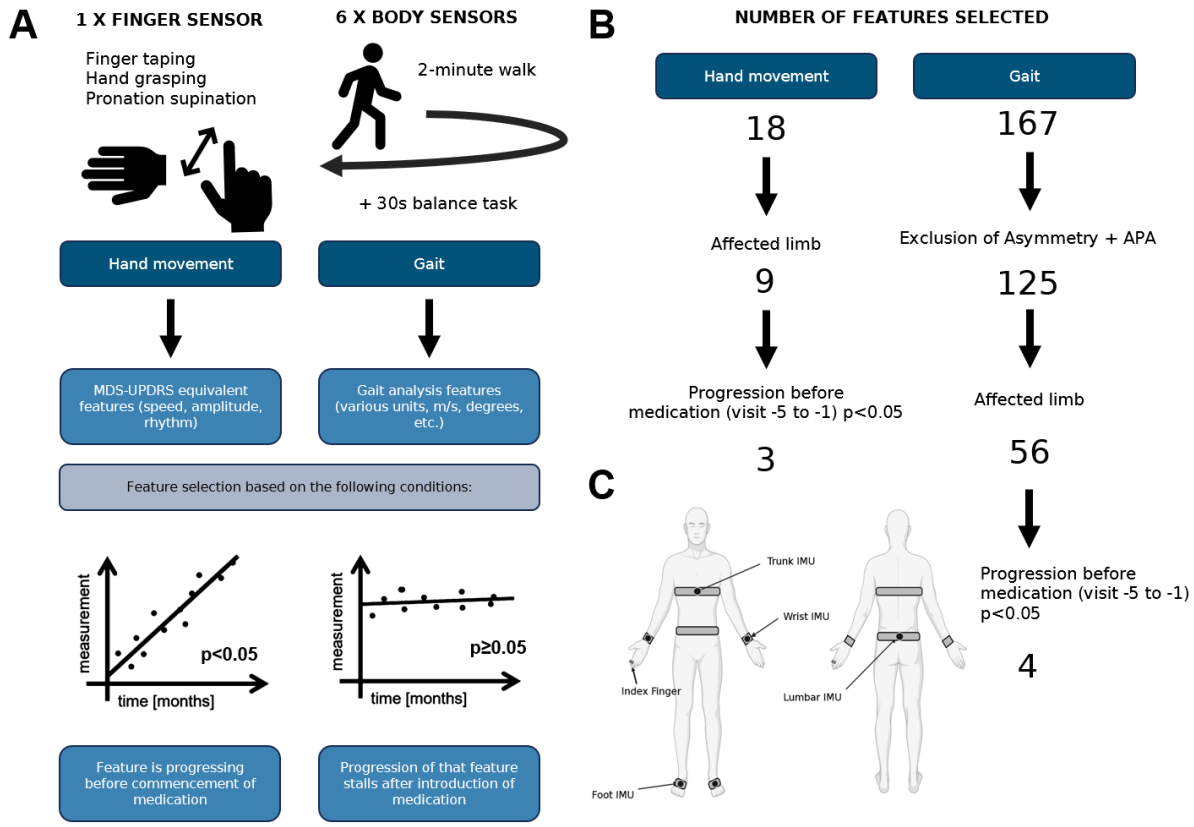


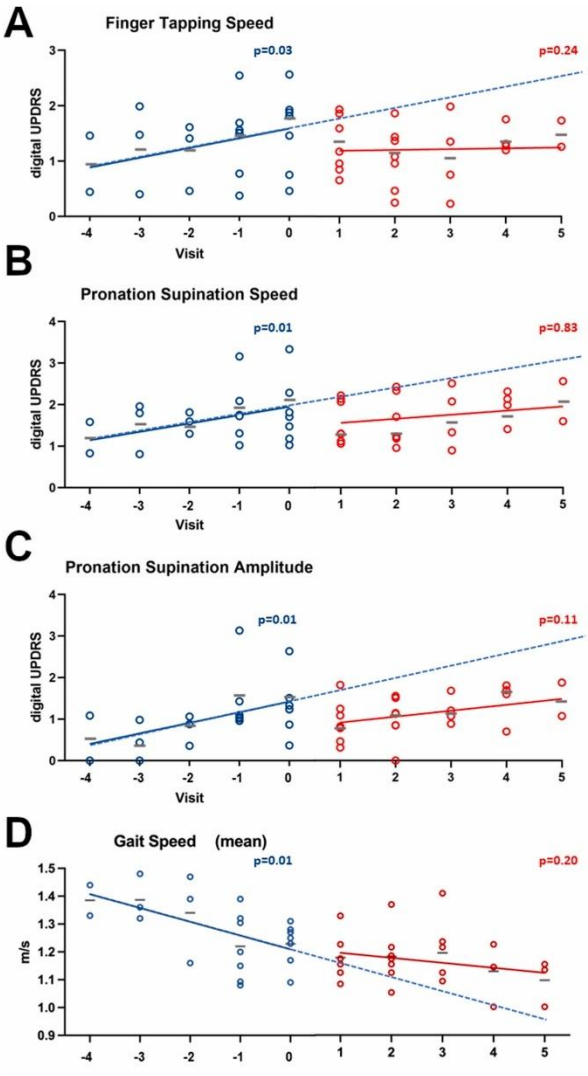
Figure 3.2 Data processing and selection of features included in the analysis. (A) The measurements were obtained by applying wearable accelerometer and gyroscope sensors in three different tasks: gait (2 min walk), balance, and bradykinesia subset of MDS-UPDRS. (B) Dimensionality of the dataset was reduced by applying feature selection. (C) Placements of sensors on the body. APA = Anticipatory Postural Adjustments.

3.3 Results

Three bradykinetic and three gait features were found to significantly progress with time prior to onset of medication (Fig. 3.3). 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 dopaminergic medication, there was a flattening of progression observed for each measure (i.e. acute shift towards normal values) followed by a flattening of the curve indicating that further progression was masked. 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. 3.4).

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).



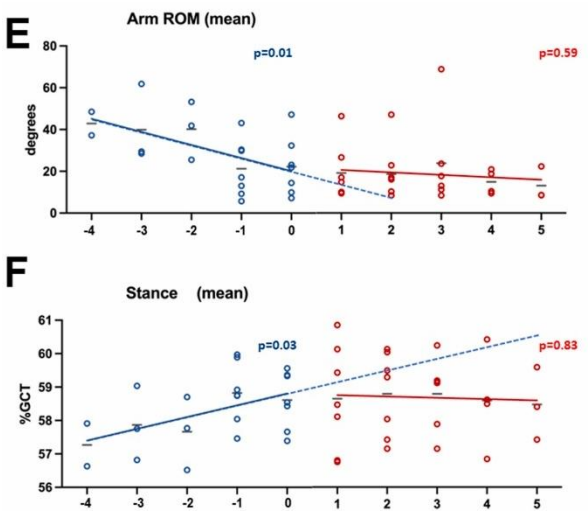
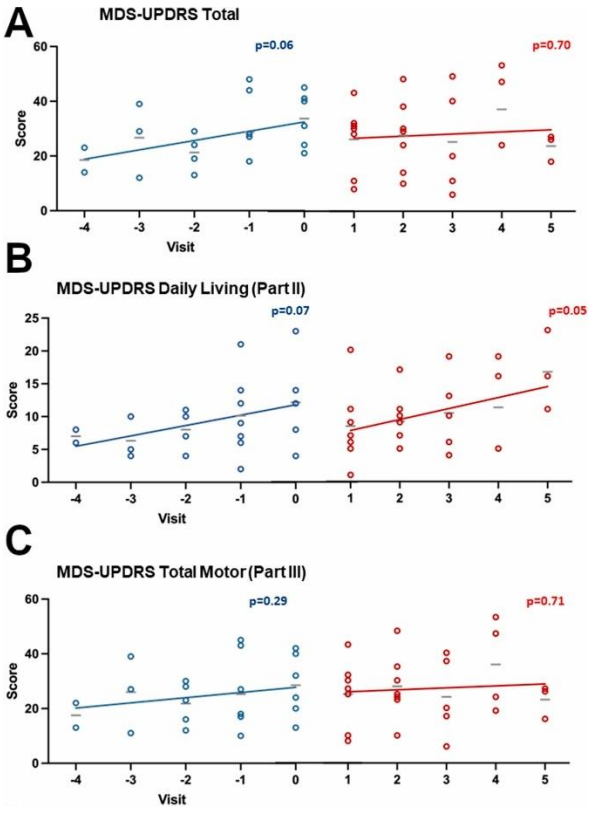


Figure 3.3 Progression of finger tapping speed (A), pronation supination speed (B), pronation supination amplitude (C), gait speed (D), arm ROM (E) and the duration of stance phase (F) over time, before and after introducing medication. Visits are at three-monthly intervals. The significance levels are presented for the linear regression line of best fit. Dotted line shows an extrapolation of the pre-medication condition, added to illustrate the change in trajectory 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.



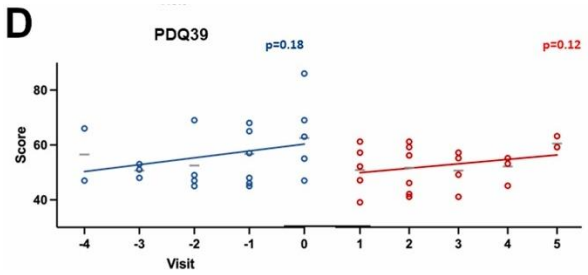


Figure 3.4 Progression of total MDS-UPDRS (A), MDS-UPDRS Motor Aspects of Experiences of Daily Living (Part II) (B), Motor MDS-UPDRS (Part III) (C) and PDQ 39 (D) scores, before and after introducing medication. Visits are at three-monthly intervals. The significance levels are presented for the linear regression line of best fit. MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale, PDQ 39 = Parkinson's Disease Questionnaire 39.

3.4 Discussion

3.4.1 Introduction of antiparkinsonian medication masks progression signals

Wearable sensors were employed to obtain detailed quantitative measurements of bradykinesia in early-stage, unmedicated PD patients. This approach facilitated the identification of six distinct features exhibiting progressive changes over time. The initiation of antiparkinsonian medication resulted in a flattening of progression in these features. In all cases, a shift towards normalcy was observed, followed by a masking of the previously discernible progression. The knowledge of which features' progression is masked by levodopa is extremely valuable for setting the correct outcomes in clinical trials. It is possible that a non-significant result may arise not due to a lack of genuine clinical phenomenon but because of the choice of metrics.

Logistically, it is very difficult to design and conduct a study that would offer a three-monthly resolution of analysis, capture enough visits before and after the start of pharmacotherapy, and allow participants to commence the medication of their own volition. Only a few studies have explicitly published analyses of this phenomenon. Mancini et al. aimed to identify objective measures of postural control that can sensitively track the progression of disease before treatment onset. Thirteen subjects with newly diagnosed PD and twelve healthy controls were assessed over one year using accelerometer-based metrics of trunk sway during quiet standing. The findings indicated that medio-lateral sway metrics, particularly medio-

lateral jerk were more sensitive than antero-posterior metrics in detecting PD progression. Only minimal changes in MDS-UPDRS motor scores were observed (Mancini et al., 2012a). Direct comparison of our findings to those of Mancini et al. can be challenging due to methodological differences. These include the use of distinct sensor systems (six body-worn IMUs vs a single lumbar IMU) and differing feature calculation methods. Nevertheless, both studies demonstrate the utility of accelerometer-derived features in tracking disease progression among unmedicated patients. Additionally, both investigations suggest that the MDS-UPDRS may lack sufficient sensitivity to definitively capture this progression.

WATCH-PD was a study that attempted to measure progress in the de-novo PD population using a range of wearable sensor systems. The in-clinic assessment was done through the same six IMUs with the same protocol (2-minute walk and sway task) and analytical software (Mobility Lab, APDM) and at similar time points (baseline, and then every 3 months up to a year). The commencement of medication was voluntary. WATCH-PD investigators estimated that about 40 of the recruited 82 de-novo patients would start medication during the study period. When published, this dataset could provide the most relevant replication of our analysis. At the time of submission, however, only cross-sectional data was available (Adams et al., 2023).

3.4.2 Physiological changes after the introduction of medication

Features extracted by this analysis have a strong biological basis. 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 (Bologna et al., 2018; Poewe et al., 2017). The tasks require adequate movement planning and sensory integration, leading to the sequential execution of repetitive movements both in small (finger-tapping) and larger (pronation supination) muscle groups (Berardelli et al., 2001). Finally, the analytical models look at three distinct aspects of the movement execution (speed, amplitude and rhythm).

Features of gait are classically known to be affected in the progression of Parkinson's disease (Mirelman et al., 2019), with impairments in the speed of walking, step length (Pistacchi et al., 2017), amplitude of arm swing (Mirelman et al., 2016), and postural control (Mancini et al., 2012b) becoming evident over the course of the disease. The features identified

in this study have specifically been seen to progress in early PD patients (Pistacchi et al., 2017; Wilson et al., 2020). Levopoda improves gait abnormalities in PD patients (Curtze et al., 2016), as seen with selected gait features of the de novo patients. Despite a number of studies identifying postural sway as being affected in early PD, only a small number of sway features are highlighted as progressing significantly on the group-mean level. A reason for this could be the small sample size masking more sway features from being selected. Additionally, the effect of levodopa on sway is contradictory and can in fact cause further instability; no effect of levodopa on sway was identified in this study. Further work will be required to determine whether sway features do, in fact, progress at this early de novo stage and what effect levodopa may have.

3.4.3 Research applications

The masking of progression signals by symptomatic medication is a major problem for clinical trials. This is particularly evident for the new drug candidates aimed at slowing PD pathology. Such trials rely on being able to accurately track disease progression, so that a beneficial effect of a medication can be observed as a reduction in the progression rate. There are some possible ways to tackle this problem. Trials of drug candidates aimed at slowing disease progression could be limited to de novo participants. Arguably, these are the people with the most to gain from these agents. However, most patients are now started on medication automatically, and the de novo population is a small minority, thus making the recruitment to such trials challenging. The generalisability of trial results to a wider PD population could also be difficult.

Another option would be to stop antiparkinsonian medication for study assessments. Although levodopa is a symptomatic treatment, it does have some enduring effects, as discussed earlier in this chapter. 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 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 (Bredemeyer et al., 2022; Lu et al., 2019).

3.4.4 Limitations and future directions

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 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 not have 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. Nevertheless, the pattern in our results is clear: there is a progression in multiple movement-related biomarkers in de novo PD patients, but this is obscured following the commencement of symptomatic medication.

3.4.5 How were patients involved in the study?

The results of the study were presented during PPI meetings in Oxford, Newbury, and Chichester. Participants expressed interest in a digital tool that could provide them with objective data to help assess their gait and upper body slowness of movement. This would prove especially useful when deciding the time to start antiparkinsonian medication. A few recounted that they found it difficult to make decisions about their treatment due to a lack of objective data. At the time of their PD clinic, participants felt the need for a more comprehensive assessment, which the wearable sensors could provide. Participants also noticed that the features presented in this chapter had a direct effect on their lives, especially slowness of finger tapping, gait speed, and arm range of motion. Overall, the system was judged as simple, non-invasive, and effortless to wear. It was pointed out, however, that such a system could be too complex to use at home without support and supervision.

3.5 Conclusions

In this chapter, a masking of disease progression after the commencement of medication was demonstrated. Whilst small in sample size, this preliminary dataset addresses the previously unresearched aspect of PD pathology.

4

Kinematic Data Help Predict Future Fallers in Parkinson's Disease: A Five-Year Prospective Study

The work from this chapter was published in *npj Digital Medicine - Predicting future fallers in Parkinson's disease using kinematic data over a period of 5 years December 2024 7(1) DOI: 10.1038/s41746-024-01311-5*

4.1 Introduction

Falls are a common problem for people living with PD (Crouse et al., 2016; Fasano et al., 2017; Grimbergen et al., 2004; Okuma, 2014; Pelicioni et al., 2019), with consequences including injuries, hospitalisations, and reductions in mobility, quality of life, and life expectancy (Paul et al., 2017; Thurman et al., 2008; Walker et al., 2013; Wielinski et al., 2005). A review of 22 studies estimated that 60% (range 35 to 90%) of all people living with PD will experience at least one fall in their lifetime (Allen et al., 2013), with 39% falling multiple times. In contrast with PSP, falls in PD are relatively infrequent in the first years of diagnosis. More than 60% of newly diagnosed PD patients will remain falls-naïve by 36 months' follow-up (Lord et al., 2016), with the majority of falls occurring in the postural instability and gait disturbance (PIGD) phenotype (Lord et al., 2017; Pelicioni et al., 2019). This means that the selection of patients with the highest risk of falls remains challenging and requires the identification of several demographic and disease-related factors (Bloem et al., 2001; Foreman et al., 2011; Kerr et al., 2010; Michałowska et al., 2005).

4.1.1 Estimating risk of falls – clinical metrics

Clinical risk factors can be categorised into demographic, disease-related and falls-related features. The first group assesses information available from the medical records, such as disease duration (Lord et al., 2017), phenotype (Pelicioni et al., 2019), polypharmacy (Richardson et al., 2015) age and gender (Gale et al., 2016), although the last two have not been consistently associated with risk of falls in PD population (Murueta-Goyena et al., 2024). Specific PD-related features include freezing (Paul et al., 2014), gait impairment (Wilczyński et al., 2021), dyskinesia (Paul et al., 2014), abnormal axial posture (Latt et al., 2009), increased walking variability (Lord et al., 2016), cognitive impairment (Camicioli and Majumdar, 2010), and postural instability (Lindholm et al., 2015; Mak and Auyeung, 2013). A history of having already fallen is the strongest and most obvious predictor of future falls (Allen et al., 2013). A fall also produces a range of related risk factors such as fear of falling (Grimbergen et al., 2013), self-perceived disability (Almeida et al., 2015), reduced activity and use of assistive mobility devices (van der Marck et al., 2014).

At present, evaluating these factors usually relies on the assessment of the clinician (Pickering et al., 2007; Visser et al., 2003). This requires adequate time to collect and synthesise a range of information from multiple sources (history-taking, family interviews, hospital, and GP records) as well as extensive expertise and experience for a detailed neurological examination. Access to specialist centres that could provide such a level of care is limited. Even then, the most structured clinical assessments are prone to subjectivity and variability, as discussed in Chapter 2. Reliance on the presence of falls-related factors is only possible in patients who already experienced a fall, which excludes falls-naïve patients – a population who arguably has the most to gain from preventive interventions. A more objective way to prospectively identify prospective fallers is desirable. This chapter will focus on gait and posture abnormalities that could lead to an increased risk of falls. An objective, sensor-based assessment of these will be discussed.

4.1.2 Gait cycle assessment

The cycle consists of two distinct phases: stance and swing (Camathias et al., 2020). The stance phase, encompassing roughly 60% of the total gait cycle time (GCT), starts with initial

contact of the observed foot with the ground and concludes when the toe is taken completely off the ground. The swing phase, occupying the remaining 40% of the GCT, commences at toe-off and terminates upon foot strike. Within stance, three support phases can be identified. The initial double support phase, lasting 14-20% of stance, commences with a heel strike and concludes when the contralateral foot leaves the ground. Subsequently, the single support phase, constituting 60-72% of stance, occurs as the contralateral leg swings through the air. Finally, terminal double support, encompassing another 14-20% of stance, begins with the contralateral foot contacting the ground and ends with the toe-off of the observed foot. For simplicity, initial and terminal double support phases can be combined as total double support.

Every gait cycle starts with the index foot making initial contact with the ground. The angle between the floor and the foot at that moment is referred to as the foot strike angle. Then, the loading response begins throughout the initial double support phase. This marks the transfer of weight into the index foot, as the function of the contralateral limb moves from shock absorption to support. The mid-stance phase begins when the opposite foot is lifted off the ground, swung and touching the ground. This single support phase can be divided into initial mid-stance and terminal mid-stance. When the opposite foot touches the ground, the pre-swing phase for the index foot commences, which also marks the beginning of the second double support phase. Finally, the toe of the index foot is lifted off the ground (forming the toe-off angle), and the swing phase begins. This single support phase can be further divided into initial, mid and terminal swing phases for the index foot (Fig. 4.1).

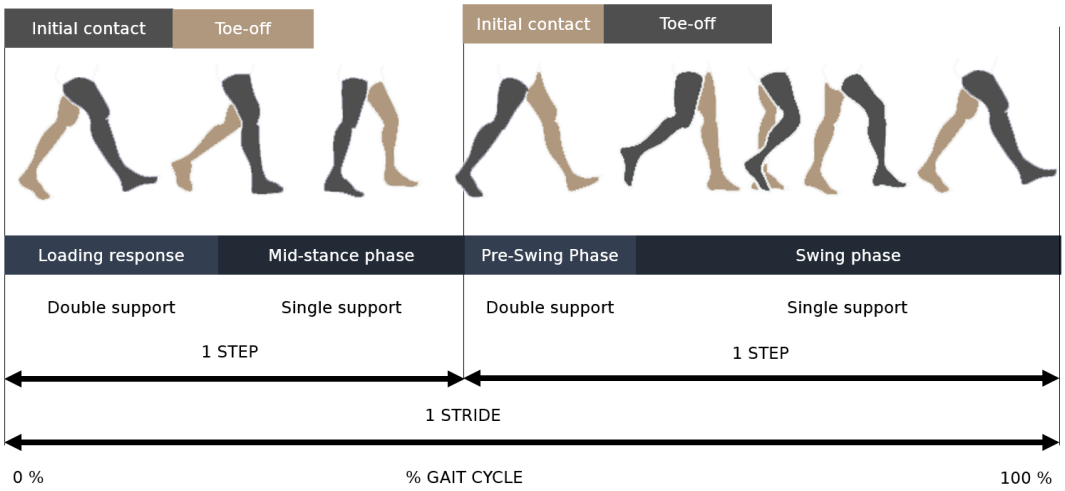


Figure 4.1 Breakdown of gait cycle phases, figure adapted from (Camathias et al., 2020).

Several potential features of the gait cycle disturbance could be linked to an increased risk of falls. Reduced arm swing is seen in PD (Espinoza-Araneda et al., 2023; Navarro-López et al., 2022; Sterling et al., 2015), due to bradykinesia and rigidity. Lower stride length is an amplitude reduction and a feature of bradykinesia, resulting from an inability to produce adequate movement initiation cues in the basal ganglia (Lewis et al., 2000; Morris et al., 1996). Clinically assessed reductions in stride length and overall gait cycle (gait speed) have been linked to increased risk of falls in previous studies (Hausdorff, 2009; Lai et al., 2022). PD patients also exhibit lower ability to maintain balance on one leg only, as evidenced by lower single support phase and longer double support phase (Chevrier et al., 2022). The ability to balance on one leg has been identified as a significant predictive factor of falls resulting in injuries in an older population (Riemann and Schmitz, 2012; Vellas et al., 1997). Reduced foot strike angle at the beginning of the double support phase has also been observed in PD (Monaghan et al., 2023). This adaptive mechanism reduces the weight load and absorbed shock of the index foot and has been used to distinguish PD fallers and non-fallers (Araújo et al., 2023). Reduced propulsion force for the toe-off angle is evident in PD (Monaghan et al., 2023; Schlachetzki et al., 2017) and could cause lower foot lifting, which increases the likelihood of stumbling on objects and falling. Variability of these features could also be an important predictor of falls (Ayoubi et al., 2014; Hausdorff et al., 2001).

4.1.3 Postural balance assessment

Postural sway, sometimes referred to as standing balance, is the body's ability to maintain an upright posture during quiet standing on a firm, flat surface. The centre of mass (COM) is controlled in the anterior-posterior (AP, coronal) and mediolateral (ML, sagittal) planes. When participants stand still with feet set apart, their base of support (feet) is narrower than the shoulder width. With the feet in a fixed position on the floor, the situation resembles an inverted pendulum. Constant muscle activations are required to counteract rotational forces and maintain equilibrium. Small corrective coronal and sagittal movements are therefore physiologically expected. Gravitational torque forces exerted on the ankle are counteracted by

stiffness (muscles and connective tissue) and neural commands (tonic and top-down signals). During the sway task, participants utilise muscle force to move the centre of pressure in phase with COM. To achieve that, several somatosensory signals are integrated in the CNS, which subsequently sends corrective commands. Proprioception, vestibular apparatus and muscle tone are used as afferent inputs. Reliance on visual correction is obscured by asking participants to close their eyes during the task. Loss of balance occurs when COM moves outside the level of support, and the body musculature is unable to stop the unexpected coming to the ground.

Participants with PD exhibit jerkier sway (Dewey et al., 2014; Mancini et al., 2012b, 2011), higher sway area (Stylianou et al., 2011), higher velocity of sway (Dewey et al., 2014; Mancini et al., 2012b) and larger root means square error ellipse area (Perera et al., 2018). This could be due to difficulty organising and integrating sensory inputs by the basal ganglia (Brown et al., 2006), which could lead to the ineffectiveness of fine-tuning postural control (Rinalduzzi et al., 2015). Inaccurate and noisy detection of COM has also been observed in PD (McKay et al., 2021). Increased stiffness in the ankle joints and leg muscles can lead to rigidity and jerky movements of the COP (Burleigh et al., 1995; Rinalduzzi et al., 2015). Postural instability is widely considered one of the most important clinical predictors of falls in PD (Cardoso et al., 2023; Crouse et al., 2016; Tsai et al., 2023; Viseux et al., 2020), and therefore it can be hypothesised that larger values of sway features should hold predictive value of future falls in the population studied in this chapter.

4.1.4 Estimating risk of falls – sensors

Wearable sensors are an increasingly popular way of identifying aforementioned gait and sway problems in people with PD (De Vos et al., 2020b; FitzGerald et al., 2018; Sotirakis et al., 2022). Data obtained from sensors and analysed using automatic feature selection strategies can distinguish between people with PD and other Parkinsonian disorders (De Vos et al., 2020b), track the progression of motor symptoms in PD (Sotirakis et al., 2023), and identify motor symptoms such as tremor and freezing of gait (Huang et al., 2023). Recent research, summarised in Table 4.1, demonstrates significant improvements in falls risk estimation using digital monitoring systems and clinical assessments. Wearable sensors can improve risk

assessment by analysing gait characteristics (Hasegawa et al., 2019; Ullrich et al., 2023) and gait variability (Hausdorff et al., 2001; Weiss et al., 2014). This emphasises the importance of continuous digital monitoring over subjective and singular clinical observations. A study by Weiss et al. (2014) demonstrated that a single lumbar accelerometer worn for three days can prospectively identify future fallers within a year (Weiss et al., 2014). However, this remote passive monitoring paradigm may be logistically challenging for many clinical set-ups. Whether a shorter, standardised, clinic-based gait and balance assessment can be utilised to predict future fallers remains unknown.

Table 4.1 Summary of literature on predicting future falls in Parkinson's Disease using digital devices. PIGD = Postural Instability & Gait Disturbance Phenotype

Study	Aim	Task	Results	Follow-up [months]
Digital device + clinical assessment				
(Pelicioni et al., 2019)	Contrast fall rates between PIGD and non-PIGD PD subtypes. Clinical assessment used to classify phenotypes.	113 PD (67 PIGD, 46 non-PIGD) Prospective study; recording of gait-related features using triaxial accelerometer; also measured other disease and clinically relevant features.	PIGD more likely to fall overall with more falls related to FOG, balance-related falls, and at home.	12
(Shah et al., 2023)	To investigate if digital measures of gait collected via passive monitoring of daily activities, over a week, increases the discriminative ability to predict future falls compared to fall history alone. Mixed group of fallers and non-fallers at time of recruitment.	34 PD (17 fallers, 17 non-fallers). 3 IMU sensors for one week of passive gait monitoring. Followed up by email every 2 weeks for a year for self-reported falls.	Inertial sensors worn on the feet and lumbar level for 7 days provided measures of gait pace, variability and turning that increased the ability to predict future falls in addition to history of previous falls	12
(Ullrich et al., 2023)	To compare different data aggregation approaches and machine learning models for the prospective prediction	35 PD patients with foot-worn sensors performing unsupervised 40m walking tests over two weeks. Falls	The highest accuracy (74%) was achieved with a Random Forest Classifier applied to the passive monitoring gait data, when	3

	of fall risk using gait parameters derived either from continuous real-world recordings or from unsupervised gait tests. (FallRiskPD study). Mixed fallers and non-fallers.	were self-reported for 3 months.	aggregating all walking bouts and days of each participant	
(Tsai et al., 2023)	To evaluate the feasibility of combining disease-specific and balance-related measures as risk predictors for future falls in patients with PD. Mixed fallers and non-fallers.	95 patients underwent postural sway measurements and clinical functional scores. Followed up patients to determine if fall occurred after 6 months.	Fall history, Tinetti balance, sway length, velocity, and gait score associated with future falls.	6
Digital devices only				
(Weiss et al., 2014)	Whether metrics derived from three-day continuous recordings were associated with fall risk. Non-fallers followed for one year to evaluate predictors of transition from non-faller to faller.	67 non-falling PD patients wore an accelerometer on lower back for 3 days.	Higher than median gait variability was associated with higher risk of progressing to fall in the follow-up period	12
(Ma et al., 2022)	To evaluate gait features associated with higher risk of falls. Mixed fallers and non-fallers (both groups had history of falls)	51 PD patients assessed using six wearable gyroscopes and accelerometers during 7m timed up and go task	Increased gait variability directly correltated with increased risk of falls	6
(Sturchio et al., 2021)	Whether kinematic features can predict increased risk of falls. Most participants already falling at the time of recruitment.	26 PD patients with orthostatic hypotension assessed using two-minute walk test, timed up and go and postural sway tasks	Waist sway, jerkiness, centroidal frequency predicted increased risk of falls	6

(Greene et al., 2021)	Whether the number of falls can be estimated from kinematic parameters. Mixed datasets of falling and non-falling participants were used.	71 patients with PD compared with healthy older population. Participants were assessed using a three-meter timed up and go test with two sensors placed on shins	There was a moderate correlation between sensor data and actual fall counts	Up to 6

4.1.5 Objectives

The aim of the present study was to determine whether data acquired by wearable sensors during a brief test in clinic can objectively predict the risk of falling in people with PD, based solely on sensor data and clinicodemographic variables. Machine learning methods will be used to analyse baseline wearable sensor measurements taken from participants at their first study visit, together with follow up data at 24 and 60 months that specified whether the participant had had any falls by each time point. Additionally, in order to deliver clinically interpretable model results, we explored the most important kinematic features for the identification of potential fallers.

4.2 Methods

4.2.1 Participants

In this chapter, participants from both medicated and unmedicated PD groups were used (Chapters 2 and 3). The recruitment was conducted as outlined in Chapter 2. Additional eligibility criterion for this analysis was the ability to perform walking and balance tasks independently (without any assistance or walking device). Patients with any history of falls at the time of recruitment were excluded. Falls status was verified by surveying participants and their families during clinical history taking and additionally confirmed by medical records, where possible. A full flowchart of participant selection and follow-up is available in Figure 4.2. Participants lost to follow-up were not considered in the fall prediction modelling at 60 months.

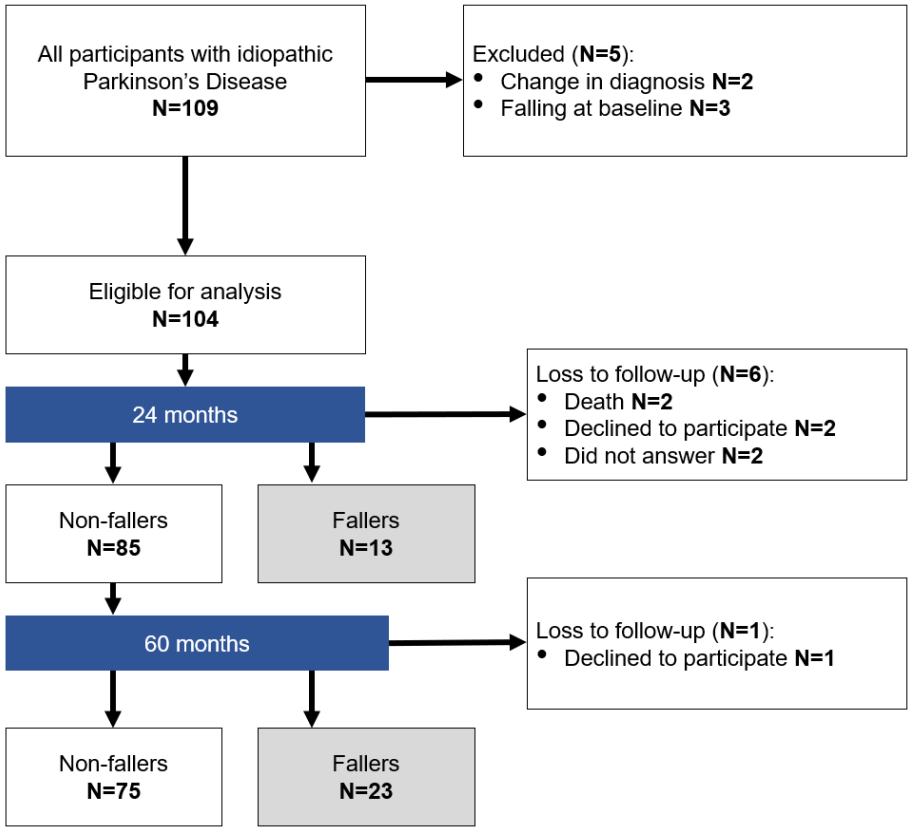


Figure 4.2 Follow-up flowchart. Data were analysed at two time points: 24 and 60 months.

4.2.2 Baseline gait and sway tasks

At their initial visit, participants were asked to walk for two minutes on a straight level surface in a 15m-long corridor, making 180-degree turns when necessary. For measurement of postural sway, participants were instructed to stand still for 30 seconds, keeping their eyes closed, with a standard inter-malleolar distance. An experienced clinical researcher was standing or walking on each participant's side to ensure safety when performing the tasks. As described in Chapter 3, an array of 6 IMU sensors (OpalTM, APDM, Portland, Oregon, USA) was utilised to collect kinematic data. The sensors were placed on both wrists and feet, the sternum, and the lumbar region, using elastic straps. Each sensor provided raw accelerometer, gyroscope, and magnetometer data at a sampling frequency of 128Hz. Clinical history and neurological examination were also obtained. This was done by an MDS-certified researcher using history-taking, MDS-UPDRS (Movement Disorder Society, 2003), Hoehn and Yahr (H&Y) (Hoehn and Yahr, 1967), The Parkinson's Disease Questionnaire (PDQ39) (Peto et al., 1998) and EQ-5D-5L (UK version) (Herdman et al., 2011) scales.

4.2.3 Falls reporting

A fall, similarly to previous studies (Allen et al., 2013; Araújo et al., 2023; Vitorio et al., 2023), was defined as an unintentional event that results in a loss of balance and subsequent complete coming to the ground or some lower level, not due to a major intrinsic event or overwhelming hazard. At each follow-up time point we recorded simply whether or not the participant had experienced any falls up to that point. Falls data for the 24-month time point were obtained from records of in-person visits in OxQUIP study. Due to the COVID-19 pandemic, some participants ended the study prior to the 24-month time point; for those participants (N=13), telephone follow-up was conducted. 60-month falls follow up data were obtained from two sources. Some participants had continued in research clinics where fall status was recorded. For participants no longer attending research clinics at 60 months (N=57), telephone follow-up was conducted. Where available, additional confirmation of the time of fall was obtained from hospital and General Practitioner (GP) records.

4.2.4 Data reduction and analysis

The MobilityLab software (APDM, Portland, Oregon, USA) was used to automatically extract kinematic features. All features related to stride length were normalised by dividing by the participant's height in metres. All right and left limb-specific features were relabelled as Ipsilateral and Contralateral, relative to the side of symptom onset.

We explored the ability of baseline kinematic data to predict the onset of falls by 24 months, and 60 months after the baseline visit. For each time point, fallers were identified, and the dataset prepared for analysis by splitting the population into fallers and non-fallers. The majority class (non-fallers) was resampled to match the size of the minority class (fallers) prior to any further analysis. The collinearities present in the dataset necessitated a feature selection pipeline, before applying machine learning techniques. An independent sample comparison of all features was performed using a Mann-Whitney U test, to identify the features that demonstrate the most significant difference between fallers and non-fallers. A 1% False Discovery Rate (FDR) was used to correct for multiple comparisons.

Five machine learning models were then trained to distinguish between fallers and non-fallers at the 24- and 60-month time points: Logistic Regression (LR), Random Forest (RF),

Support Vector Machine (SVM), Elastic Net (EN), and XGBoost. The dataset was split into training and testing sets using stratified 5-fold cross-validation to ensure a balanced representation of fallers and non-fallers in each fold. Hyperparameter tuning was performed for each model using Optuna, an automatic hyperparameter optimization framework. The objective function aimed to maximize the average accuracy across the cross-validation folds. The search space for hyperparameters was defined using Optuna's distributions, including categorical, log-uniform, integer, and uniform distributions, tailored to each classifier's specific hyperparameters. Model performance was evaluated using accuracy, precision, recall, F1 score, and area under the receiver operating characteristic curve (ROC-AUC). The ROC curves were generated by averaging the false positive rates (FPR) and true positive rates (TPR) across the cross-validation folds using linear interpolation. 95% confidence intervals for the ROC-AUC were calculated using bootstrapping.

To assess the impact of including baseline clinico-demographic information: age, disease duration, total MDS-UPDRS part III score, and MoCA score were incorporated as additional features. Four distinct feature sets were evaluated for each model and time point:

a) Complete feature set including clinico-demographics

b) Complete feature set excluding clinico-demographics

c) Selected features (based on univariate testing) including clinico-demographics

d) Selected features excluding clinico-demographics

The best-performing models for each feature set and time point were identified based on the average ROC-AUC across the cross-validation folds. The actual and predicted fall status for each participant was recorded for the best models. A full compliance checklist with TRIPOD-AI reporting guidelines is available in Appendix 1.

4.3 Results

One hundred and four participants were eligible for inclusion in the analysis. Demographic and clinical information are shown in Table 4.2. Thirteen participants had fallen by 24 months, and by the 60-month follow-up, this had increased to 23.

Table 4.2 Summary of demographic data for the studied sample

Parameter	Fallers	Non fallers
N	23	74
Age (IQR)	71 (6.5)	65 (9.8)
Sex (Male/Female)	14/9	42/32
Months since diagnosis (IQR)	100.4 (98)	30.4 (47.3)
Side of Symptom onset (Right/Left)	10/13	34/40
Dominant side (Right/Left/Ambidextrous)	22/0/1	61/10/3
Montreal Cognitive Assessment Score (MoCA)	27 (3.5)	27 (3)

4.3.1 Variability of walking most consistently predicts future falls

Table 4.3 highlights features demonstrating significant differences between fallers and non-fallers at a 60-month horizon. These differences were tested with the Mann-Whitney U test and corrected using a 1% False Discovery Rate (FDR). Specifically, the analysis revealed significant differences in features related to walking and postural variability in terms of standard deviation between fallers and non-fallers, in addition to mean stride length and age at enrolment. These included the variability of single and double limb support phases, swing, and terminal double support phase durations, as well as the variability of postural sway acceleration. Spearman correlation analysis revealed an expected correlation between swing and stance and at least several other features. The notable non-correlated features were Trunk Range of Motion on the sagittal plane, step duration and toe-off angle variability (Fig. 4.3).

Table 4.3 Mann-Whitney U statistics for significant features for the 60-month time window, after correcting for multiple comparisons using 1% False Discovery Rate.

Feature	Mann Whitney U	P value
Lower Limb - Toe Off Angle IP (Degrees) [Std]	1140	0.0018
Lower Limb - Single Limb Support IP (%GCT) [Std]	1201.5	0.0002
Lower Limb - Single Limb Support CO (%GCT) [Std]	1142.5	0.0017
Lower Limb - Stance IP (%GCT) [Std]	1173.5	0.0006
Lower Limb - Stance CO (%GCT) [Std]	1148	0.0014
Lower Limb - Step Duration CO (S) [Std]	1077	0.0012

Lower Limb - Stride Length IP (M) [Mean]	457	0.0024
Lower Limb - Stride Length CO (M) [Mean]	464	0.003
Lower Limb - Swing IP (%GCT) [Std]	1173.5	0.0006
Lower Limb - Swing CO (%GCT) [Std]	1148	0.0014
Lower Limb - Terminal Double Support CO (%GCT) [Std]	1158.5	0.001
Trunk - Sagittal Range of Motion (Degrees) [Std]	1126	0.0028
Age [years]	1124.5	0.0028

IP = Ipsilateral, CO = Contralateral limbs, Std = Standard Deviation.

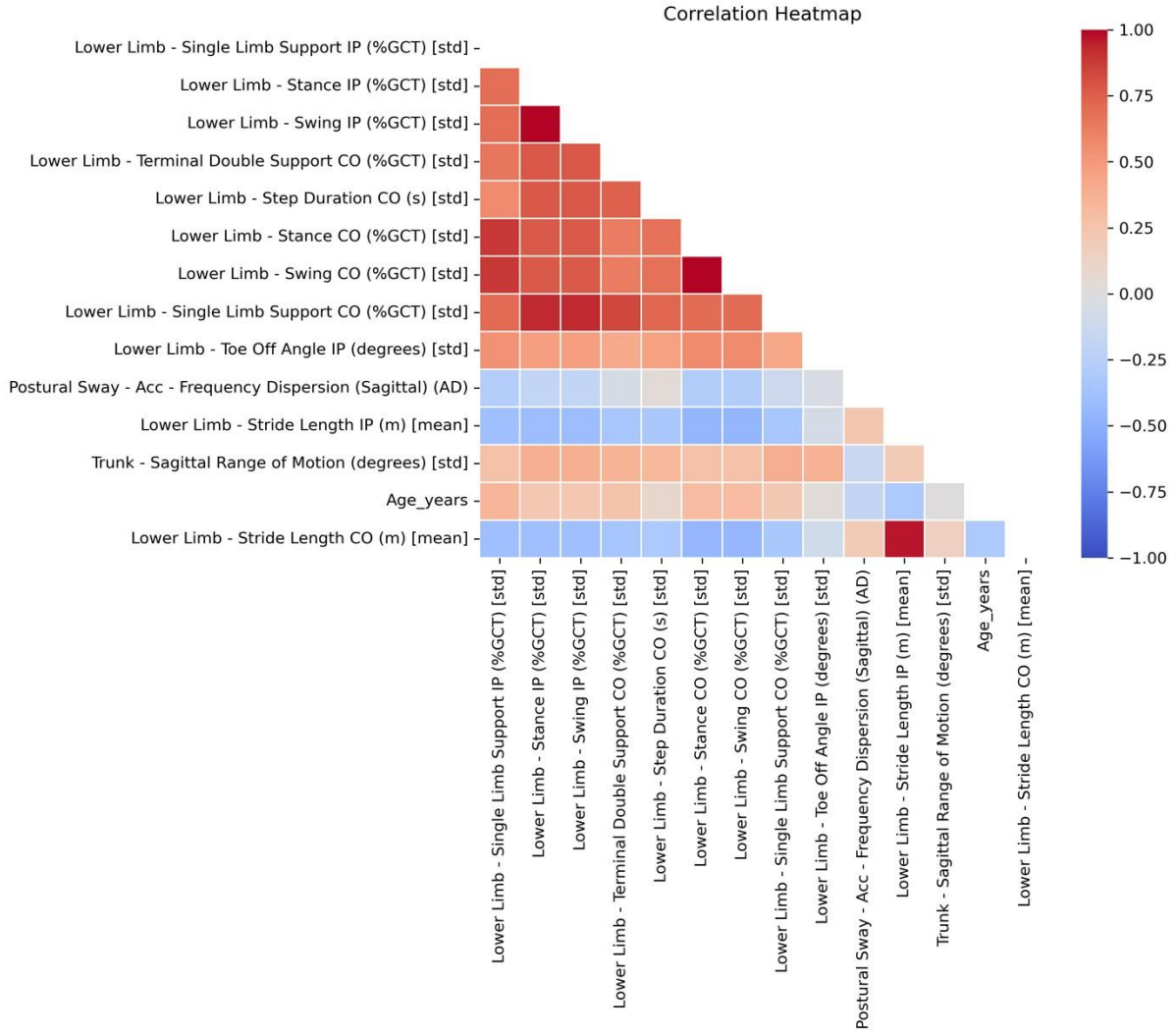


Figure 4.3 Correlation matrix of the selected features.

4.3.2 Shorter time horizons yield more reliable predictions in three classifier models

Using IMU data from baseline, we aimed to predict future faller status at 24-, and 60-months' time horizons using classification algorithms. Evaluation of classification benchmarks for Logistic Regression, Random Forest, Support Vector Machines, Elastic Net and XGBoost is presented in Table 4.4. These models were used as they are known to deal well with collinearities that were expected to be apparent in the datasets. For each model, 5-fold cross validation was performed on the set of features. The dataset was randomly split in 5 sets; 4 sets are used to train the model, and the remaining one is used as an independent validation set. In order to explore the predictive power of a model trained with kinematic data only, it was compared to a combined one containing both kinematic and clinicodemographic data. The model performance was further tested before and after the feature selection process. This resulted in four different feature sets at which the model was trained, as discussed in the methods section. Receiver operating characteristic curves (ROC) for the models are presented in Figure 4.4. The models revealed excellent performance (AUC>0.9, accuracy=84-92%) in the 24-month time and diverged performance in the 60-month time window. For the 60-month time window, RF trained on the selected features, including the clinicodemographic data, performed the best (AUC=0.85, accuracy=78%). Notably, only the age at enrolment was significant and included in the model and did not substantially improve the classification performance (without age: AUC=0.81, accuracy=78%).

Table 4.4 Model performance evaluation.

MODEL	HYPER-PARAMETERS	ACCURACY	PRECISION	RECALL	F1	ROC-AUC	ROC-AUC 95% CI LOWER	ROC-AUC 95% CI UPPER	TIME WINDOW (MONTHS)	FEATURE SET (ALL/SELECTED)	CLINICO-DEMOGRAPHICS INCLUDED (YES/NO)
LOG_REG	{'clf__C': 0.0031958012947468166, 'clf__max_iter': 2132, 'clf__solver': 'newton-cg', 'threshold': 0.4557782935917123}	0.92	0.883	1	0.931	0.967	0.85	1	24	all	Yes
RF	{'clf__n_estimators': 1611, 'clf__max_depth': 28, 'clf__min_samples_split': 6, 'clf__min_samples_leaf': 3, 'clf__max_features': 'log2', 'threshold': 0.3896642860695312}	0.84	0.8	1	0.876	0.967	0.85	1	24	all	Yes
XGB	{'clf__max_depth': 20, 'clf__n_estimators': 1163, 'clf__learning_rate': 0.03901758155814582, 'clf__subsample': 0.8087678236908055, 'clf__colsample_bytree': 0.3289839451991656, 'clf__min_child_weight': 1, 'clf__scale_pos_weight':15.287063329122024}	0.88	0.883	0.9	0.865	0.9	0.8	1	24	all	Yes
ELASTIC_NET	{'clf__C': 0.3539925110867631, 'clf__l1_ratio': 0.21101297273980643, 'threshold': 0.2638918207845958}	0.92	0.883	1	0.931	0.967	0.85	1	24	all	Yes
SVM	{'clf__C': 18.417379710276947, 'clf__kernel': 'linear', 'clf__gamma': 2.2066080427722197, 'clf__degree': 2, 'threshold': 0.44441217013110923}	0.887	0.883	0.933	0.891	0.967	0.85	1	24	all	Yes
LOG_REG	{'clf__C': 0.26897846822404786, 'clf__max_iter': 1303, 'clf__solver': 'sag', 'threshold': 0.20495003515533272}	0.92	0.883	1	0.931	0.967	0.85	1	24	all	No
RF	{'clf__n_estimators': 1194, 'clf__max_depth': 39, 'clf__min_samples_split': 11, 'clf__min_samples_leaf': 6, 'clf__max_features': 'log2', 'threshold': 0.43943314192880295}	0.88	0.883	0.933	0.891	0.967	0.85	1	24	all	No
XGB	{'clf__max_depth': 65, 'clf__n_estimators': 1884, 'clf__learning_rate': 0.017265755823930758, 'clf__subsample': 0.6041990595039644, 'clf__colsample_bytree': 0.5142043041554412, 'clf__min_child_weight': 1, 'clf__scale_pos_weight': 6.407414089018169}	0.84	0.833	0.9	0.836	0.867	0.65	1	24	all	No
ELASTIC_NET	{'clf__C': 25.770874102861562, 'clf__l1_ratio': 0.8026110897984811, 'threshold': 0.25392576867921995}	0.92	0.883	1	0.931	0.967	0.85	1	24	all	No

SVM	{'clf__C': 199.80152798543273, 'clf__kernel': 'linear', 'clf__gamma': 0.5911733057714688, 'clf__degree': 2, 'threshold': 0.4353063683428038}	0.92	0.883	1	0.931	0.967	0.85	1	24	all	No
LOG_REG	{'clf__C': 2.3962368855975105, 'clf__max_iter': 1113, 'clf__solver': 'sag', 'threshold': 0.23651968528040954}	0.92	0.883	1	0.931	0.967	0.85	1	24	selected	Yes
RF	{'clf__n_estimators': 1928, 'clf__max_depth': 59, 'clf__min_samples_split': 5, 'clf__min_samples_leaf': 3, 'clf__max_features': 'log2', 'threshold': 0.4515188890070245}	0.84	0.85	0.933	0.865	0.933	0.8	1	24	selected	Yes
XGB	{'clf__max_depth': 28, 'clf__n_estimators': 396, 'clf__learning_rate': 0.03537805263742179, 'clf__subsample': 0.7287082880755303, 'clf__colsample_bytree': 0.6170373651127488, 'clf__min_child_weight': 1, 'clf__scale_pos_weight': 11.949015906299234}	0.92	0.883	1	0.931	0.867	0.65	1	24	selected	Yes
ELASTIC_NET	{'clf__C': 16.149733534459454, 'clf__l1_ratio': 0.19522477318519407, 'threshold': 0.1401421587363022}	0.92	0.883	1	0.931	0.967	0.85	1	24	selected	Yes
SVM	{'clf__C': 0.003422465684088275, 'clf__kernel': 'linear', 'clf__gamma': 0.7059288175689866, 'clf__degree': 3, 'threshold': 0.4137859111229378}	0.92	0.883	1	0.931	0.967	0.85	1	24	selected	Yes
LOG_REG	{'clf__C': 0.9202071986835539, 'clf__max_iter': 1912, 'clf__solver': 'liblinear', 'threshold': 0.26101694468144165}	0.92	0.883	1	0.931	0.967	0.85	1	24	selected	No
RF	{'clf__n_estimators': 1815, 'clf__max_depth': 56, 'clf__min_samples_split': 5, 'clf__min_samples_leaf': 3, 'clf__max_features': 'log2', 'threshold': 0.4604917632766704}	0.88	0.883	0.933	0.891	0.933	0.8	1	24	selected	No
XGB	{'clf__max_depth': 25, 'clf__n_estimators': 1441, 'clf__learning_rate': 0.0877673357652389, 'clf__subsample': 0.8754395360252616, 'clf__colsample_bytree': 0.5187519517473727, 'clf__min_child_weight': 1, 'clf__scale_pos_weight': 10.16525861519159}	0.92	0.883	1	0.931	0.867	0.65	1	24	selected	No
ELASTIC_NET	{'clf__C': 2.5476395643027065, 'clf__l1_ratio': 0.6852508515754069, 'threshold': 0.3440449604112895}	0.92	0.883	1	0.931	0.967	0.85	1	24	selected	No
SVM	{'clf__C': 0.005921083452658545, 'clf__kernel': 'linear', 'clf__gamma': 1.9669215856292483, 'clf__degree': 5, 'threshold': 0.356745127065022 5}	0.92	0.883	1	0.931	0.967	0.85	1	24	selected	No
LOG_REG	{'clf__C': 0.005642086188488141, 'clf__max_iter': 714, 'clf__solver': 'sag', 'threshold': 0.545600680242065}	0.74	0.893	0.59	0.678	0.676	0.215	0.978	60	all	Yes

RF	{'clf__n_estimators': 1533, 'clf__max_depth': 38, 'clf__min_samples_split': 21, 'clf__min_samples_leaf': 4, 'clf__max_features': 'sqrt', 'threshold': 0.5023481832290014}	0.742	0.808	0.72	0.72	0.778	0.453	0.975	60	all	Yes
XGB	{'clf__max_depth': 69, 'clf__n_estimators': 1756, 'clf__learning_rate': 0.0005433709951144718, 'clf__subsample': 0.9905655545211147, 'clf__colsample_bytree': 0.45750649846014624, 'clf__min_child_weight': 1, 'clf__scale_pos_weight': 9.061855669409242}	0.698	0.741	0.68	0.673	0.71	0.323	0.967	60	all	Yes
ELASTIC_NET	{'clf__C': 0.06088388286812541, 'clf__l1_ratio': 0.37512236048430037, 'threshold': 0.5165499764027633}	0.74	0.92	0.58	0.652	0.694	0.227	0.984	60	all	Yes
SVM	{'clf__C': 0.001577389532512457, 'clf__kernel': 'poly', 'clf__gamma': 16.718616090057317, 'clf__degree': 3, 'threshold': 0.5226084282511976}	0.607	0.833	0.31	0.432	0.459	0.022	0.919	60	all	Yes
LOG_REG	{'clf__C': 0.005393294307290948, 'clf__max_iter': 852, 'clf__solver': 'liblinear', 'threshold': 0.5297318355566222}	0.718	0.86	0.55	0.635	0.666	0.205	0.978	60	all	No
RF	{'clf__n_estimators': 1720, 'clf__max_depth': 56, 'clf__min_samples_split': 6, 'clf__min_samples_leaf': 4, 'clf__max_features': 'sqrt', 'threshold': 0.5167365470221826}	0.7	0.764	0.68	0.682	0.738	0.39	0.975	60	all	No
XGB	{'clf__max_depth': 40, 'clf__n_estimators': 1523, 'clf__learning_rate': 0.0010866361219808275, 'clf__subsample': 0.9896743893751013, 'clf__colsample_bytree': 0.6835330180368607, 'clf__min_child_weight': 1, 'clf__scale_pos_weight': 3.498467330178081}	0.718	0.827	0.64	0.666	0.658	0.239	0.975	60	all	No
ELASTIC_NET	{'clf__C': 0.042849851622108616, 'clf__l1_ratio': 0.21058763953491505, 'threshold': 0.49941009313963086}	0.696	0.833	0.59	0.624	0.772	0.332	1	60	all	No
SVM	{'clf__C': 0.030846198418782673, 'clf__kernel': 'poly', 'clf__gamma': 4.998807815398268, 'clf__degree': 4, 'threshold': 0.5506922994372738}	0.567	0.7	0.23	0.313	0.5	0.152	0.867	60	all	No
LOG_REG	{'clf__C': 0.7744747828794467, 'clf__max_iter': 2142, 'clf__solver': 'liblinear', 'threshold': 0.5045445296312534}	0.784	0.9	0.71	0.742	0.81	0.41	1	60	selected	Yes
RF	{'clf__n_estimators': 1858, 'clf__max_depth': 53, 'clf__min_samples_split': 16, 'clf__min_samples_leaf': 3, 'clf__max_features': 'log2', 'threshold': 0.5990544046759362}	0.784	0.96	0.63	0.712	0.848	0.519	1	60	selected	Yes
XGB	{'clf__max_depth': 28, 'clf__n_estimators': 137, 'clf__learning_rate': 0.00761805803260816,	0.784	0.92	0.68	0.719	0.812	0.479	0.992	60	selected	Yes

	'clf__subsample': 0.777047964205214, 'clf__colsample_bytree': 0.7429468604292498, 'clf__min_child_weight': 9, 'clf__scale_pos_weight': 15.477691016018344}										
ELASTIC_NET	{'clf__C': 0.6049813921417699, 'clf__l1_ratio': 0.7428944242438275, 'threshold': 0.4884238159906587}	0.807	0.9	0.75	0.778	0.8	0.388	1	60	selected	Yes
SVM	{'clf__C': 0.006733533204648455, 'clf__kernel': 'linear', 'clf__gamma': 0.0007107851511125971, 'clf__degree': 5, 'threshold': 0.5192326659196909}	0.807	0.96	0.67	0.76	0.83	0.509	1	60	selected	Yes
LOG_REG	{'clf__C': 0.7213436763518033, 'clf__max_iter': 923, 'clf__solver': 'sag', 'threshold': 0.5015732300425518}	0.807	0.927	0.71	0.76	0.828	0.452	1	60	selected	No
RF	{'clf__n_estimators': 1085, 'clf__max_depth': 33, 'clf__min_samples_split': 5, 'clf__min_samples_leaf': 4, 'clf__max_features': 'log2', 'threshold': 0.6121568440899445}	0.784	0.96	0.63	0.712	0.812	0.482	1	60	selected	No
XGB	{'clf__max_depth': 70, 'clf__n_estimators': 1247, 'clf__learning_rate': 0.0034069563196480945, 'clf__subsample': 0.5264444276434259, 'clf__colsample_bytree': 0.43372511563091226, 'clf__min_child_weight': 2, 'clf__scale_pos_weight': 14.309653925856248}	0.784	0.96	0.63	0.712	0.788	0.428	1	60	selected	No
ELASTIC_NET	{'clf__C': 7.240237570756752, 'clf__l1_ratio': 0.16377671036581645, 'threshold': 0.6030452811371839}	0.807	0.96	0.66	0.74	0.772	0.432	1	60	selected	No
SVM	{'clf__C': 0.04781126512504679, 'clf__kernel': 'linear', 'clf__gamma': 0.027506361130383673, 'clf__degree': 2, 'threshold': 0.5305281243732878}	0.807	0.92	0.71	0.773	0.8	0.401	1	60	selected	No

LOG_REG = Logistic Regression, RF = Random Forest, XGB = eXtreme Gradient Boosting, ROC = Receiver Operating Characteristic, AUC = Area Under Curve.

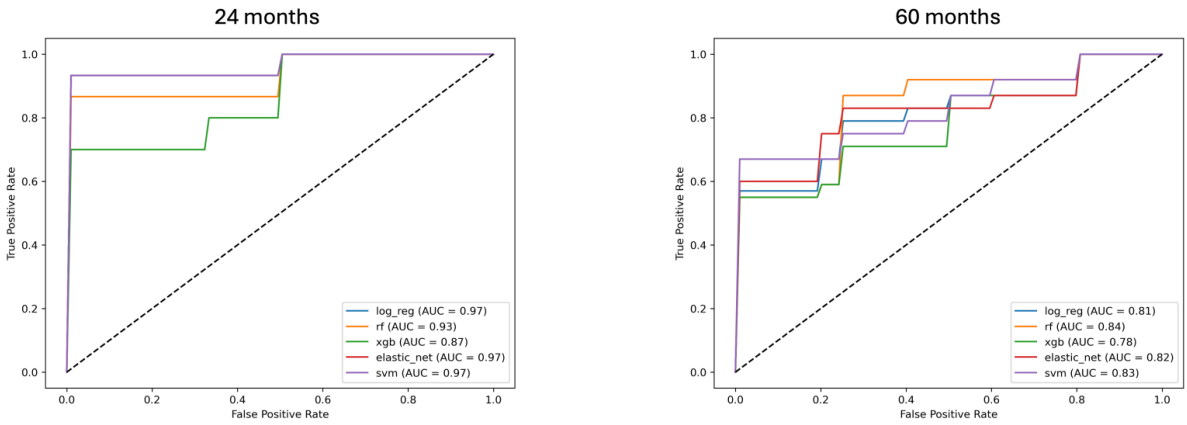


Figure 4.4 Receiver Operating Characteristic (ROC) curves. Five classifiers were evaluated in the study: Logistic Regression, Random Forest (RF), Support Vector Machine (SVM), Elastic Net (EN) and XGB (eXtreme Gradient Boosting) at each of the 24 and 60 months. The performances of the best models are illustrated. AUC = Area Under the Curve.

4.3.3 Comparison with clinical scales and risk factors

Several commonly employed questionnaires and clinical scales were used to capture disease severity and self-perceived decline in mobility. There was a difference between prospective fallers and non-fallers in terms of their baseline Motor (Part III) score of the MDS-UPDRS, Hoehn and Yahr stage, PDQ39 (mobility) and EQ-5D-5L index scores (UK version) (Figure 4.5). The baseline PDQ39 mobility items that were significantly worse in the group of participants who started falling included difficulties with walking 100 yds, $\frac{1}{2}$ mile, getting around the house, getting around in public, fear of falling, need of assistance when going out, and the associated feeling of being confined to the house.

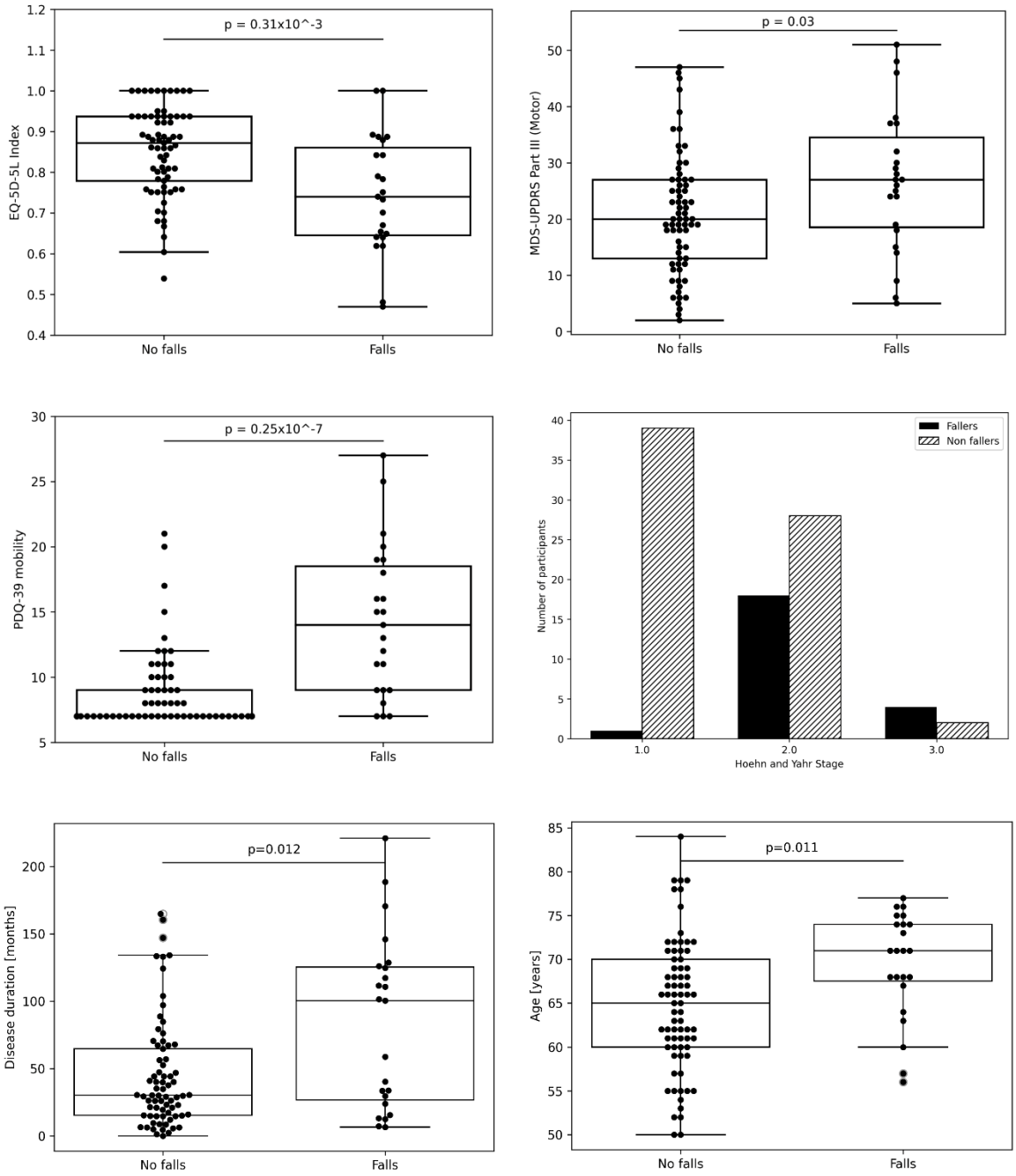


Figure 4.5 Comparison of clinically assessed risk factors of falls in the studied population. PDQ39mobility = sum of items 4 to 10 of PDQ39 questionnaire (self-rated walking, fear of falling, confidence in getting around).

4.4 Discussion

Our study presents a digital approach to predicting first falls in patients with PD using wearable sensor data. This five-year prospective study was designed to investigate the predictive capability of kinematic data derived from two standard motor clinical assessments, namely, a two-minute walking task and a 30-second postural sway examination. We assessed three machine learning classifier models for their ability to identify people with PD, with no prior history of falls, who are at risk of falling within 2 and 5 years.

4.4.1 Model performance evaluation

Of the five models assessed, the Random Forest classifier outperformed the other models at 60 months. At 24 months, Logistic Regression, Elastic Net, and Support Vector Machine models were the best performing. All five classifiers were most accurate at 24 months. A decline in accuracy at longer time points is a general feature of forecasting and is therefore to be expected to some degree, but it is a reasonable assumption that variability in disease progression rate is a contributory factor here. The kinematic data on which the analysis was based was all derived from a single visit for each participant, and it therefore contains no individual information about progression.

Other studies have reported different rates of falls (Almeida et al., 2015; Lindholm et al., 2015; Pelicioni et al., 2019; Tsai et al., 2023). For the non-falling subset of Weiss et al., 14 out of 67 (20.9%) experienced their first fall in a 12-month follow-up period (Weiss et al., 2014). In a more recently published extension of the LONG-PD study, by 24 months, 32 out 846 (3.7%) participants were falling "persistently", which was defined as still experiencing falls in at least 2 annual follow-ups (Chase et al., 2023). The discrepancy in falling rates between studies can be explained by differences in disease stage at recruitment, recall bias, and varying proportions of PIGD and tremor-dominant phenotypes. The patients in our study were relatively early in the course of their disease, mostly at Hoehn and Yahr stages 1 or 2, and it is therefore expected that our event indices fall on the lower end of the spectrum seen in the literature. In keeping with other studies, metrics such as baseline Hoehn and Yahr disease stage (Lord et al., 2016), MDS-

UPDRS Part 3 (Mak and Auyeung, 2013), PDQ39 mobility (Almeida et al., 2015; Balash et al., 2007) , and general self-reported disability (Lindholm et al., 2015) (EQ-5D-5L index) proved to be significantly worse in people who experienced their first fall within the follow-up period of this study.

Feature selection was undertaken to identify the key variables that distinguish people with Parkinson's with and without risk of falling. Mean stride length was found to be an important predictor of future falls. This finding aligns with previous research suggesting that reduced stride length may be a compensatory mechanism for deteriorating dynamic balance in PD, leading to a slow, shuffling gait (Morris et al., 1996) and eventually increased risk of falls (Lai et al., 2022). As the disease progresses, patients rely more on an increase in cadence to achieve effective ambulation at the same walking and tuning speed, with stride length remaining low (Bayle et al., 2016). To increase the length of steps, an increased cognitive processing is required and can be aided by external pacing, e.g. through visual cues (Lewis et al., 2000). This means that a lower stride length observed in this chapter could be due to a higher degree of disease pathology.

All the other important predictors were standard deviations of a range of gait parameters, i.e. measures of variability. Pathology in the basal ganglia function disrupts the normal patterns of neural activity responsible for smooth and coordinated movements, resulting in increased variability in gait parameters (Hausdorff et al., 1998), although the exact neural pathway remains to be established. Proprioceptive deficits, which impair the sense of joint position and movement, can make it difficult for individuals with PD to accurately perceive and adjust their gait in response to changes in terrain or balance challenges (Camargo et al., 2024). This impaired sensory feedback can further contribute to increased gait variability. Muscle weakness, fatigue, and rigidity can impact the force generation and coordination required for normal gait. These motor impairments can manifest as decreased stride length, reduced arm swing, and difficulty initiating or terminating steps, all of which can contribute to increased standard deviations of gait features (Huang et al., 2017). Executive function deficits, attentional impairments, and difficulties with dual tasking can all interfere with the cognitive resources required for maintaining a steady and consistent gait pattern (Rochester et al.,

2005). The significance of walking variability in relation to falls has been well established in previous research (Hasegawa et al., 2019; Hausdorff et al., 2001; Springer et al., 2006; Weiss et al., 2014) exploring falling both in healthy old adults and people living with neurological disorders. Accurate measurement of walking variability is a key advantage of wearable systems since such variability is difficult to estimate with the naked eye.

4.4.2 Clinical implications

Predicting fall risk enables targeted medical intervention for prevention. Several treatment programs and strategies exist (Allen et al., 2022; Canning et al., 2014; Liu et al., 2022), including exercise (Morris et al., 2017, 2011; Sherrington et al., 2017), fall-prevention education (Cattaneo et al., 2019; Ward et al., 2004), medication reviews (Bor et al., 2017; Hauser et al., 2016; Henderson et al., 2016; Huang et al., 2012), and complex care interventions (Age UK, 2023; Dent et al., 2019; Logan et al., 2021). Reports show that fall prevention strategies can be successful (Allen et al., 2022; Cordani, 2023; Guirguis-Blake et al., 2018; Lamb et al., 2005; Lord and Close, 2018) when offered at an earlier stage, especially before the first fall. However, a comprehensive falls prevention programme is resource intensive (Logan et al., 2021). A model that predicts who does or does not need to be offered such a programme could help in population health and social care planning. This could ensure that scarce resources are more optimally allocated. Predictive models could also be used in clinical trials. Potential pharmaceutical falls prevention agents are currently being investigated (Neumann et al., 2021). Our findings could enhance participant selection for these trials, ensuring resources are directed toward those at greatest risk within the study timeframe. One of the main focuses of this study was to develop patient-centric diagnostic and prognostic tools. The method used in this chapter delivers accurate prediction of fall risk, while the brevity of the assessment minimises the burden on patients.

4.4.3 Limitations and future work

While this study offers valuable insights into the potential for using wearable sensors and machine learning to predict fall risks in patients with PD, it is important to

acknowledge the limitation posed by the small sample size. With only 104 participants, the generalisability of the findings may be constrained. A larger and more diverse sample would be necessary to validate these results and ensure that the predictive models are robust across different populations. Therefore, future research with a broader participant base is essential to fully understand and apply these predictive tools in clinical settings. The real-life utility of the study could also be further explored in future trials by randomising participants into intense or standard falls prevention programmes based on their baseline sensor-based falls risk assessment. In that, a reduction in fall indices in the intervention arm of such study could further support the external validity of our models.

Additionally, this study did not compare its predictive model with other established clinical fall risk prediction models. This was done to establish whether falls risk can be derived specifically from sensor data and assessor-independent clinicodemographic variables such as age. While this approach provides a more objective assessment, it should be noted that many purely clinical scales are still in routine clinical use. Examples include Falls Risk Assessment Tool (FRAT), which uses recent falls, medication, psychological wellbeing and cognitive status as inputs, and Morse Falls Scale, which assesses history of falling, number of medical diagnoses, use of ambulatory aid, intravenous therapies, mental status and the use of mobility aids. A future study could directly compare these scales in a head-to-head observational trial.

Another major limitation of the study is its reliance on participant recall of fall occurrence as the ground truth for the classifier algorithms. In the same vein, while telephone follow-ups offer a convenient method for reporting falls and can facilitate broader participation, they may lack the precision of in-person visits. Recall bias in particular could potentially affect the reliability of the ground truth for falls. We attempted to mitigate this limitation in several ways. First, we derived falls metrics from history taking obtained by a trained clinician, as well as through self-reported questionnaires and recorded clinical communications. Whenever possible, we sought confirmation of the fall, or lack thereof, through collateral history. Finally, times and fall characteristics were confirmed by contemporaneous clinical records whenever possible. To ensure a real-life utility, our classifier model also needs to be prospectively validated

by an independent study, ideally as part of routine clinical assessment. This would investigate whether the accuracies presented in this analysis can be generalised to a more heterogeneous population.

4.4.4 How were patients involved in this study?

Prediction of falls was highlighted as a critical research area by both patients seen in clinic and patient and carer members of the PPI group. Both individuals with PD and their carers emphasized the importance of this research in planning and managing their care. Their insights and experiences were instrumental in shaping the study's objectives and methodology, ensuring that the research addressed real-world concerns and needs.

4.5 Conclusions

The current study contributes to the understanding of the risk of falls in PD, showing that wearable IMU kinematics and machine learning can be used to identify potential fallers in PD from a single gait and posture data collection session lasting less than 3 minutes. The study presents a comprehensive benchmarking of various models and analysis pipelines. These models were designed based on two primary objectives: First to identify people with PD at risk of falling. Second, to ensure the reliability of the models by making the data processing methods transparent to clinical experts. Early identification of potential fallers may pave the way for more targeted and effective management strategies of PD, ultimately helping to prevent life threatening falls.

5

Precise measurement of upper body bradykinesia through custom built tapping plate & wearable sensor apparatus

5.1 Introduction

Previous chapters discussed a number of commercially available bradykinesia measurement systems. APDM's Opal (Chapter 4), Great Lakes NeuroTechnologies' Kinesia (Chapters 2 and 3), PD Neurotechnology's PDMonitor, PKG Health's Personal KinetiGraph (PKG) and Sense4Care's STAT-ON have all been extensively used in many research and clinical settings, and have even been approved by some regulators (NICE, 2024). These systems are very similar in terms of hardware, comprising wearable inertial measurement units (typically including triaxial accelerometer, gyroscope and magnetometer) and an associated software package that process data into reports and features. Full access to the raw signals is, however, rarely given (see data availability statements from systems studied in Vanmechelen et al., 2023).

This can be of concern, as even a visual inspection of the graph can be helpful in initial feature and protocol validation. Raw data can also be used by competing algorithms, which means that one trial dataset can see multiple uses, without the need to recruit new participants. This is especially true with the rapid advancement of machine learning algorithms (Chen et al., 2022; Li et al., 2022; Trabassi et al., 2022). There is a need for an upper body bradykinesia motion tracking system that could produce a precise data stream in a universally used format.

To that end, a novel capacitive finger-tapping device was developed to allow for a hyper-precise, quantitative assessment of the upper body bradykinetic motor function.

The validation strategy presented in this chapter deliberately leveraged two conditions where motor function can be externally modulated in a binary fashion: medication ON/OFF states and deep brain stimulation (DBS) ON/OFF states. These conditions were specifically chosen as they produce significant and well-documented changes in motor performance that can be initiated and reversed through external intervention. The primary objective of this analysis was to evaluate whether the apparatus is capable of detecting these changes and to collect important practical feedback on its real-life use in a clinical setting.

5.2 Methods – apparatus and data processing

The tapping apparatus consisted of two 60mm diameter stainless steel plates separated by 30mm, housed in a 3D-printed case with capacitive touch sensing capabilities. The system detects finger contact through capacitive coupling, requiring minimal pressure for activation, making it suitable for patients with limited mobility as well as dry or fragile skin. A wearable sensor unit, built around a XIAO nrf52840 microcontroller with integrated accelerometer and gyroscope (LSM6DS3), was developed to measure upper limb motion between taps. Data was captured at 1KHz for the tapping plates and 104Hz for the motion sensors, with both units connecting to a computer via USB for power and data transmission.

Participants performed an alternate plate finger tapping task, tapping between the two plates with their index finger for 30 seconds. This task was chosen to assess both distal (finger flexor/extensor) and proximal (shoulder rotation/biceps & triceps) bradykinesia, while incorporating elements of precision-accuracy and basic cognitive function. Data analysis was performed using custom Python software, outputting results in a CSV format compatible with existing commercial systems.

Feature analysis of the finger tapping data focused on three main categories: basic statistics (mean, standard deviation, tap ratios), variability metrics (using Poincaré analysis for short-term and long-term variations), and entropy measures (Sample and Approximate entropy) to quantify movement regularity. Additional metrics included fatigue indicators, hesitation patterns, and upper limb motion data from the wearable

accelerometer/gyroscope unit. This comprehensive approach allowed for detailed characterization of both the temporal aspects of tapping and the spatial characteristics of arm movement between taps.

For detailed technical specifications, circuit diagrams, and comprehensive methodology, please refer to Appendix B.

5.2.1 Participants and protocol

In this chapter's experiment, participants from the DBS arm of the OxQUIP study were analysed. During pre-operative DBS clinic, patients were invited to attend the John Radcliffe Hospital to undergo off-medication examination and subsequent "on state" assessment as part of the Neuromodulation Team protocol. On the anniversary of the operation, the same assessors conduct an ON and OFF stimulation (on medication) examination using the same battery of tests.

Alternating finger tapping sensor task has been added, with patient's consent, on top of this protocol, which extended it by approximately 30 minutes.

Part of the validation experiment was to test whether the apparatus was capable of working in a clinical setting, which was more time and space sparse than the pure research clinic setting. To ensure these conditions were as closely related to the real-life as possible, participants were tested on the ward, using their bedside tables and within the time constraints of the booked neuromodulation clinic. The summary of demographic and clinical data of participants included in this analysis is available in Table 5.1.

Table 5.1 Demographic data of participants undergoing pre and post operative assessment for deep brain stimulation surgery.

Parameter median (Inter Quartile Range)	Pre-op	Post-op	
		STN	GPi
N	13	7	5
Age (IQR)	65.7 (12.5)	60.7 (15.1)	64.1 (11)
Sex (Male/Female)	6/7	3/4	4/1
Years since diagnosis	8 (3)	11 (2.5)	9 (5)
Side of Symptom onset (Right/Left)	4/9	4/3	2/3

5.2.2 Statistical analysis

Data were tested for normality using visual inspection of the histograms. No variables were normally distributed. Comparison between on and off medication was done using the Whitney U test, which makes no assumptions about the underlying data distribution and is particularly suitable for comparing two independent groups when normality cannot be assumed. Statistical significance was set at 0.05.

5.3 Results

5.3.1 Pre-operative assessment - Levodopa challenge

The speed of tapping was almost universally improved by the administration of levodopa (Table 5.2). This was evidenced by both shorter ITIs (median 259.5ms vs 350.1 ms, p=0.0001) and more taps per second (median 3.2 vs 2.5, p=0.0009). The rhythmicity of tapping also responded to the administration of antiparkinsonian medication. Standard deviation of ITI (median 28.1ms vs 38.1ms, p=0.0071), number of hesitations (median 0 vs 6.5, p=0.0011) and longer (>1s) stops or freezes have all shown a significant improvement. The Poincaré analysis revealed that, in this population, levodopa improved both short- and long-term variability, as evidenced by SD1 and SD2 metrics. The measures of complexity of the time series resulted in an unexpected finding of no difference in SampEn, scaling exponent alpha of DFA or Q stat p of autocorrelation. A further counterintuitive finding of a larger ApEn values after the introduction of medication was observed (Figure 5.1). This will be further examined in later sections of this chapter.

Global fatiguability (a core symptom of PD) was measured using two features: the difference between the maximum and minimum frequency and the difference top and bottom quartiles of the frequency spectrum. Whilst both hold theoretical capability of capturing the slowing of movement in PD, in this case neither could demonstrate any difference. In fact, the extreme values of >10Hz difference globally are unlikely to have arisen physiologically. They are most likely an artefact of multiple taps on the same plate in a short period of time, e.g. through tremor or selection error in the OFF state. The

analysis of time dwelling on the plate showed only minor differences between states. This means that the hypothesised increase in fatiguability could not be measured using proposed metrics, or that 30 seconds was not long enough to discern these phenomena in the studied PD population.

Table 5.2 Medians of finger tapping parameters observed during preoperative assessment of PD patients evaluated for Deep Brain Stimulation.

Measure	On Medication		Off Medication		P value
	Median	IQR	Median	IQR	
Inter Tap Interval Mean	259.49	96.01	350.13	74.99	0.0001
Inter Tap Interval STD	28.07	13.53	38.14	79.49	0.0071
Tap duration (dwelling) mean	53.61	23.59	68.35	26.09	0.1583
Tap duration (dwelling) STD	16.71	5.87	20.11	11.05	0.0112
Tap To ITI Ratio Mean	0.23	0.09	0.19	0.14	0.4941
Number of taps per s	3.23	1.2	2.48	0.59	0.0009
Number of Longer (>1s) Stops	0	0	0	0	0.0139
Error rate (%)	0	0	0	0.02	0.0497
SD1 (Poincaré)	25.94	17.2	37.69	76.48	0.0071
SD2 (Poincaré)	29.36	13.82	42.33	97.98	0.0173
SD ratio (Poincaré)	1.11	0.42	1.05	0.47	0.5975
Ellipse area (Poincaré)	2279	2402	3854	36198	0.0079
Qstat1 p lag1 autocorrelation	0.16	0.53	0.11	0.55	0.8018
Tap-tap change mean	0.01	0.01	0.01	0.07	0.3544
Tap-tap change STD	0.14	0.08	0.18	0.38	0.2357
Frequency mean	3.91	1.44	3.02	0.8	0.0032
Frequency STD	0.39	0.25	0.4	0.57	0.9793
Frequency maximum	5.24	1.93	3.91	2.46	0.0865
Frequency dominant	3.83	1.6	2.91	0.71	0.0014
Frequency difference first quartile to last quartile	0.56	0.3	0.4	0.46	0.2642
Frequency difference max to min	2.35	1.47	1.95	2.99	0.9104
Hesitations number	0	1	6.5	12	0.0011
Hesitations mean time	0	420	433	110	0.0009
Hesitations total time	0	517	3311	6870	0.0008
Difference in hesitations number in the first quartile to last quartile	0	0	0.5	1.25	0.0614
Approximate entropy	0.29	0.32	0.16	0.24	0.0052
Sample entropy	1.74	0.6	1.69	0.94	0.5503
Detrended Fluctuation Analysis (alpha)	0.50	0.50	0.52	0.49	0.8285
Skewness	0.15	0.6	0.72	1.75	0.1255
Kurtosis	0.17	1.66	1.58	8.21	0.0354

IQR = Inter Quartile Range, ITI = Inter Tap Interval, STD = Standard Deviation, OFF = Measurement after at least 12 hours off usual dopaminergic medication, ON = Measurement at least 1 hour after administration of usual medication. P values relate to Mann Whitney U test. Time in milliseconds.

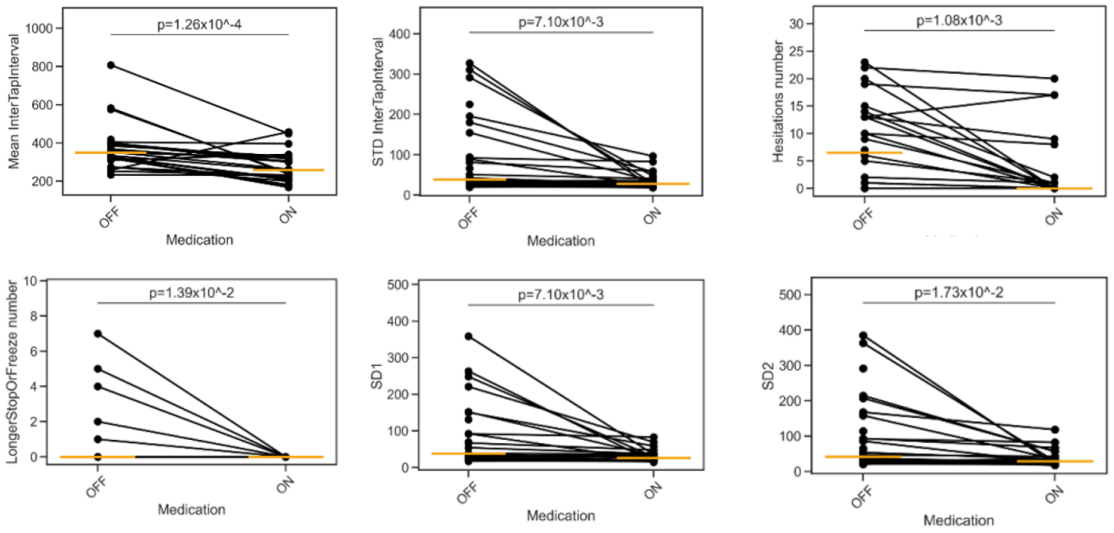


Figure 5.1 Changes in finger tapping parameters observed during preoperative assessment of PD patients evaluated for Deep Brain Stimulation. OFF = Measurement after at least 12 hours off usual dopaminergic medication, ON = Measurement at least 1 hour after administration of usual medication. P values relate to Mann Whitney U test. Datasets with too few taps (<20) were not eligible for analysis and do not have a corresponding ON/OFF state datapoint on the graph.

5.3.2 Post-operative assessment – ON/OFF Stimulation

STN stimulation improved both speed and rhythmicity of alternate finger tapping movement (Table 5.3). This was evidenced by faster ITIs (median 239.7ms vs 355.1ms p=0.07) and more taps per second (median 3.43 vs 2.63, p=0.10), although neither metric reached statistical significance. Measures of tap regularity showed larger differences between ON and OFF stimulation settings. There was a reduction in the standard deviation of ITI, from a median of 103.4ms to 28.45ms (p=0.03) and a reciprocal improvement in Poincaré analysis variability metrics SD1 (median 21.7 vs 80.7, p=0.02) and SD2 (median 33 vs 107, p=0.02). Participants' tapping was also characterised by lower error rates, fewer hesitations and longer (>1s) stops, when the stimulator was switched on. As was the case with the levodopa challenge, measures of entropy failed to

detect any meaningful change. There was a signal of fatiguability that could be appreciated by higher ranges of frequencies (median 2.53Hz min – max difference ON stimulation vs median 3.3 Hz min-max difference OFF, p=0.10). However, this was not universal, resulting in large interquartile ranges of this metric (1.35 Hz ON stim, 4.07 Hz OFF stim), resulting in a lack of statistical significance. Similarly to the levodopa challenge, it could be hypothesized that tremor played an important role in generating extremely high values of frequency (very low ITI). Of note is the heterogeneity of effect sizes of differences in studied metrics, across individuals enrolled in the study. This can be appreciated in Figure 5.2.

Participants with a stimulator targeting GPi showed a different pattern of changes (Table 5.4). There was no universal trend for shortening of mean ITI duration, with individual participants showing both improvement and mild worsening, with the majority exhibiting very little change at all (median 275.3ms vs 290ms, p=0.31). Some metrics, such as the standard deviation of the duration of dwelling on the plate, show virtually no difference under GPi stimulation (median 16.4ms vs 16.2ms). Statistical analysis revealed that, for the majority of the metrics studied any observable difference was due to chance, and not true physiological phenomenon (Figure 5.3). This could be due to changes in underlying physiology of STN and GPi stimulation, difference in demographics, worse baseline motor parameters of the recruited patients, or incorrect choice of finger tapping metrics.

Table 5.3 Medians of finger tapping parameters observed during post operative assessment of PD patients evaluated 1 year after Deep Brain Stimulation surgery with Sub Thalamic Nucleus target.

Measure	On Stimulation		Off Stimulation		P value
	Median	IQR	Median	IQR	
Inter Tap Interval mean	252.18	93.17	356.95	263.26	0.0695
Inter Tap Interval STD	32.06	41.83	119.2	201.19	0.0180
Tap duration (dwelling) mean	52.76	24.24	47.67	20.5	0.4213
Tap duration (dwelling) STD	15.45	4.21	18.42	11.44	0.2603
Error rate	0	0.01	0.03	0.19	0.0231
Tap to ITI Ratio mean	0.2	0.1	0.14	0.09	0.0180
Number of taps per s	3.4	1.06	2.55	1.75	0.0934
SD1 (Poincaré)	23.31	30.8	90.73	221.71	0.0123

SD2 (Poincaré)	40.23	39.99	134.17	188.86	0.0159
Ellipse area (Poincaré)	2433.5	9389.76	40526	170555.25	0.0123
SDratio (Poincaré)	1.24	0.48	1.2	0.42	0.6961
Longer (>1s) Stop or Freeze number	0	0	0	2	0.0078
Hesitations number	0	4	12.5	15.5	0.0674
Hesitation mean time	0	494.33	539.08	309.47	0.0310
Hesitation total time	0	2354.75	9258	11105.25	0.0146
Hesitations difference IQR	0	0	0	2	0.4911
Approximate entropy	0.39	0.41	0.08	0.29	0.1354
Sample entropy	1.73	0.57	1.51	0.56	0.1129
DFA	0.71	0.23	0.52	0.58	0.0138
Qstat1 p lag1 (autocorrelation)	0.06	0.47	0.13	0.54	0.5972
Skewness	0.5	2.53	0.95	2.55	0.6961
Kurtosis	0.27	9.01	1.7	9.72	0.6295
Tap-tap change mean	0.01	0.01	0.03	0.35	0.0180
Tap-tap change STD	0.12	0.11	0.27	1.01	0.0180
Frequency range	2.45	1.36	3.53	3.91	0.0456
Frequency IQR	0.53	0.28	0.69	0.63	0.1237
Frequency dominant	3.89	1.39	2.82	2.31	0.0628
Frequency max	5.11	2.21	6.92	2.86	0.1680
Frequency mean	3.99	1.47	3.01	2.48	0.5351
Frequency STD	0.44	0.22	0.58	0.96	0.0508

IQR = Inter Quartile Range, ITI = Inter Tap Interval, STD = Standard Deviation, OFF = Measurement with the stimulator switched off, ON = Measurement with the stimulator on. Patients were examined whilst on usual dopaminergic medication in both conditions. P values relate to Mann Whitney U test. Time in milliseconds.

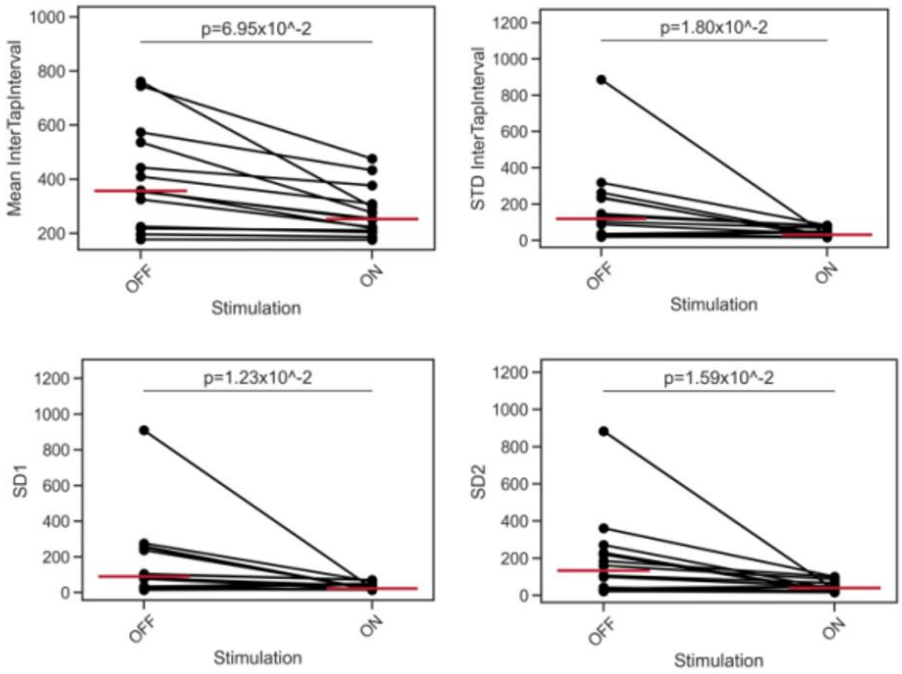


Figure 5.2 Changes in finger tapping parameters observed during post-operative assessment of PD patients with Subthalamic Nucleus Deep Brain Stimulation. OFF = Measurement with the stimulator switched off, ON = Measurement with the stimulator on. Patients were examined whilst on usual dopaminergic medication in both conditions. P values relate to Mann Whitney U test.

Table 5.4 Medians of finger tapping parameters observed during post-operative assessment of PD patients evaluated 1 year after Deep Brain Stimulation surgery with Globus Pallidus Interna target.

Measure	On Stimulation		Off Stimulation		P value
	Median	IQR	Median	IQR	
Inter Tap Interval Mean	275.28	44.45	290.02	63.39	0.3075
Inter Tap Interval STD	28.14	30.08	51.62	18.08	0.1212
Tap duration (dwelling) mean	55.11	22.20	62.93	36.92	0.4727
Tap duration (dwelling) STD	16.45	6.67	16.18	10.19	1.0000
Tap To ITI Ratio Mean	0.21	0.11	0.26	0.13	0.4274
Number of taps per s	2.93	0.65	2.90	0.38	0.6763
Number of Longer (>1s) Stops	0.00	0.00	0.00	0.00	1.0000
Error rate (%)	0.00	0.00	0.00	0.01	0.0350
SD1 (Poincaré)	27.20	15.39	37.05	24.11	0.0890
SD2 (Poincaré)	28.29	34.68	55.69	26.44	0.0890
SD ratio (Poincaré)	1.26	0.38	1.41	0.41	0.5708
Ellipse area (Poincaré)	2470	5467	5902	5640	0.1041
Qstat1 p lag1 autocorrelation	0.05	0.62	0.01	0.28	0.5205
Tap-tap change mean	0.01	0.01	0.01	0.02	0.2123

Tap-tap change STD	0.14	0.04	0.16	0.13	0.3075
Frequency mean	3.78	0.62	3.53	0.80	0.4727
Frequency STD	0.42	0.24	0.45	0.34	0.5205
Frequency maximum	4.94	1.08	4.69	1.85	1.0000
Frequency dominant	3.92	0.89	3.47	0.87	0.3847
Frequency difference first quartile to last quartile	0.51	0.30	0.46	0.42	0.9698
Frequency difference max to min	2.18	1.77	2.46	2.65	0.3847
Hesitations number	0.50	2.75	2.00	2.00	0.4344
Hesitations mean time	202	431	503	197	0.0407
Hesitation total time	202	1238	967	875	0.3343
Difference in hesitations number in the first quartile to last quartile	0	0	0	1	0.3843
Approximate entropy	0.28	0.46	0.27	0.21	0.3447
Sample entropy	1.72	0.43	1.45	0.91	0.2730
Detrended Fluctuation Analysis (alpha)	0.59	0.23	0.64	0.43	0.5205
Skewness	0.75	1.21	2.64	3.91	0.5205
Kurtosis	0.32	7.65	11.76	22.60	0.3847

IQR = Inter Quartile Range, ITI = Inter Tap Interval, STD = Standard Deviation, OFF = Measurement with the stimulator switched off, ON = Measurement with the stimulator on. Patients were examined whilst on usual dopaminergic medication in both conditions. P values relate to Mann Whitney U test. Time in milliseconds.

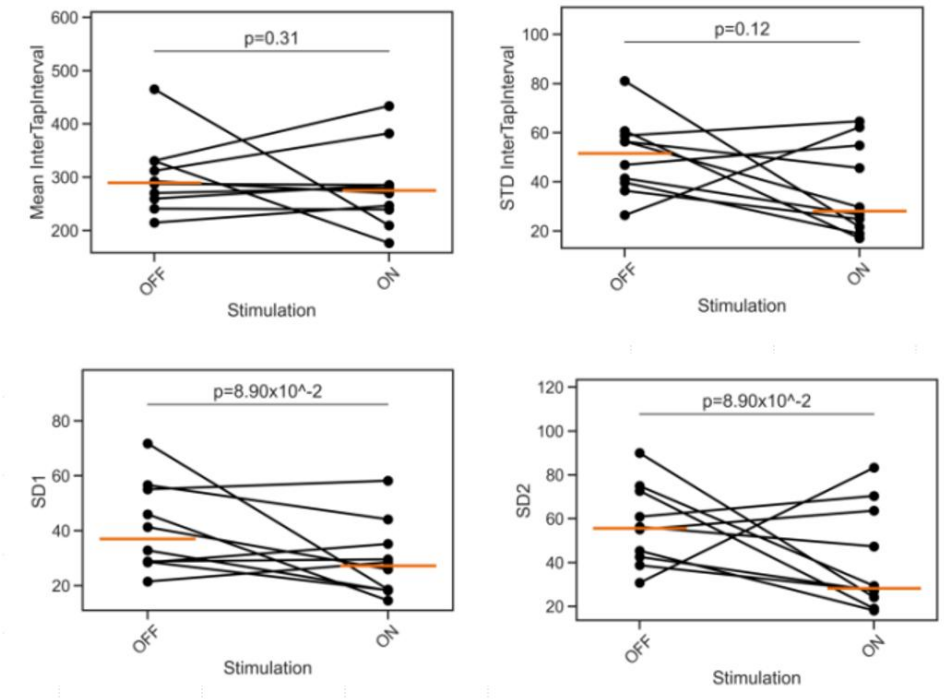


Figure 5.3 Changes in finger tapping parameters observed during postoperative assessment of PD patients with Globus Pallidus Interna Deep Brain Stimulation. OFF = Measurement

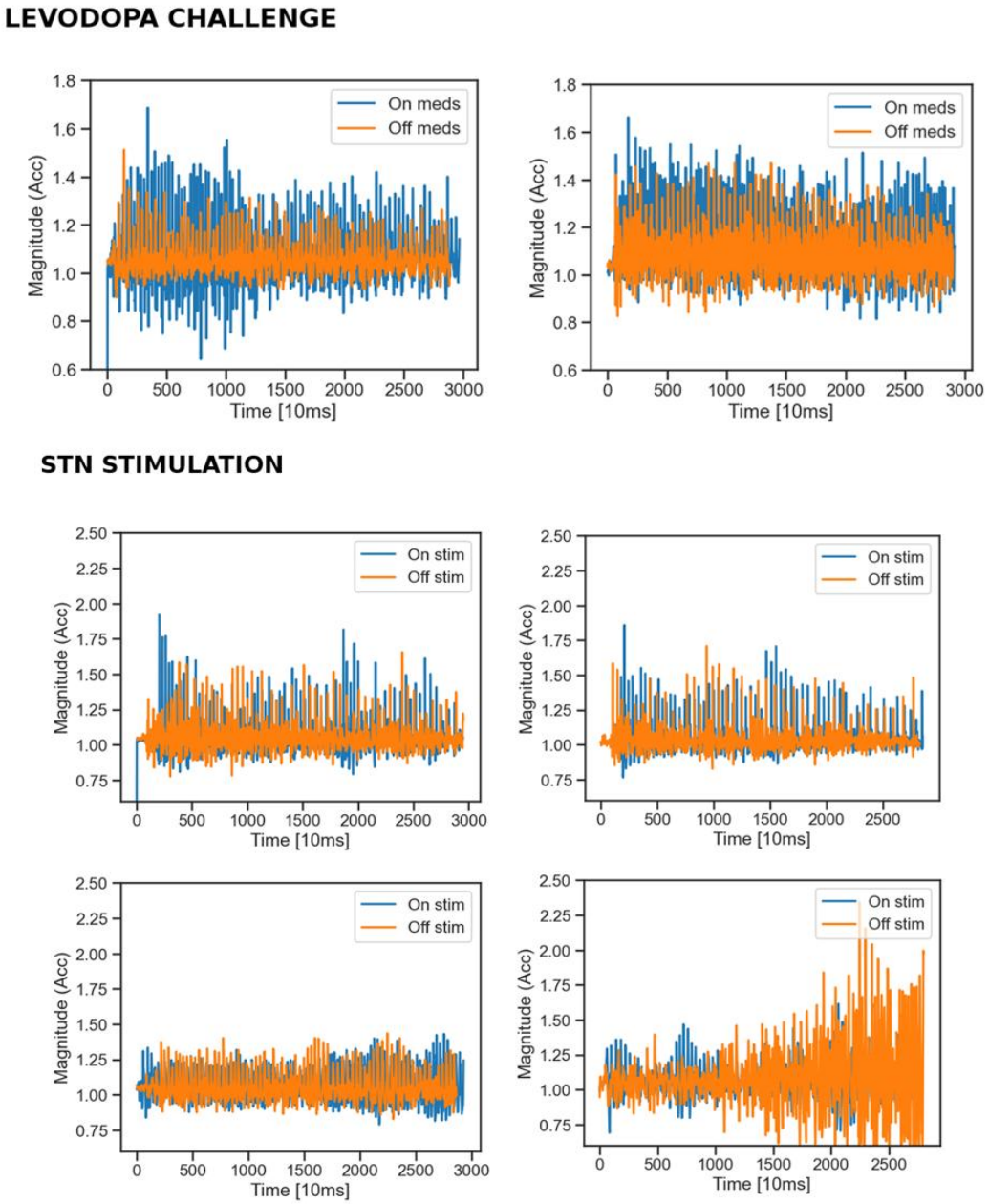
with the stimulator switched off, ON = Measurement with the stimulator on. Patients were examined whilst on usual dopaminergic medication in both conditions. P values relate to Mann Whitney U test.

5.3.3 Accelerometer data

The finger tapping device has been an evolving engineering project throughout the course of DPhil study. Thus, its full capability of accelerometer and gyroscope sampling emerged towards the later stage of participant recruitment. One participant undergoing levodopa challenge, two with STN and one with GPi were successfully tested using paired watch and plate sensors. Such a rich dataset could be examined in a variety of ways, and on different layers of complexity – as an ensemble 30s signal or by using the hyper precise finger tapping ITIs to determine the beginning and the end of each tap. The latter method could enable an interesting segmentation of the signal, allowing deep learning algorithms to be trained on large datasets of individual waves produced by accelerometer and gyroscope traces. This analysis is, however, beyond the scope of this thesis, not least due to low number of participants at the time of writing.

Individual changes in magnitude of accelerometery can be seen in Fig 5.9. There is a marked difference in the range of magnitudes after administration of medication and upon switching the stimulator, although to a lesser extent in individual cases. Traces of tremor artefacts can also be appreciated. This is especially evident in the 40100R study, where worsening dyskinetic tremor intensifies towards the end of the task, perhaps due tapping acting as a distractor to lower central involuntary movement suppression. To encapsulate these changes mathematically, a set of interquartile ranges (IQRs) were computed for each signal. For levodopa challenge participant, the administration of medication improved the range of movement as evidenced by larger IQRs in on state: 0.12 vs 0.06 for left hand, and 0.14 vs 0.09 for right hand (on vs off medication). The first STN participant had negligible IQR changes: 0.09 vs 0.09 for left hand, 0.07 vs 0.07 for right hand. The second STN participant exhibited an improvement in IQRs: 0.18 vs 0.12 for left hand and 0.13 vs 0.20 for right hand. Finally, the GPi participant noted a change in IQR 0.11 vs 0.12 for left hand, and 0.19 vs 0.24 for right hand. All metrics have been given as on and off stimulation respectively. SampEn decreased after

administration of medication 0.73 vs 0.77 for left hand, and 0.89 vs 1.13 for right hand (on vs off medication). For STN stimulation, SampEn values decreased in all but one participant: first left hand 0.61 vs 0.70, first right hand 0.56 vs 0.69, second left hand 0.68 vs 0.72, second right hand 0.66 vs 0.55. (on vs off stimulation) The improvement in SampEn for the last hand could be due to the introduction of significant tremor, which would bring more regularity to the sample (Fig 5.4). The GPi participant noted a minor but universal improvement: left hand 0.98 vs 1.08, right hand 0.56 vs 0.67 (on vs off stimulation). The ApEN was not analysed due to its instability as demonstrated in previous sections and discussion.



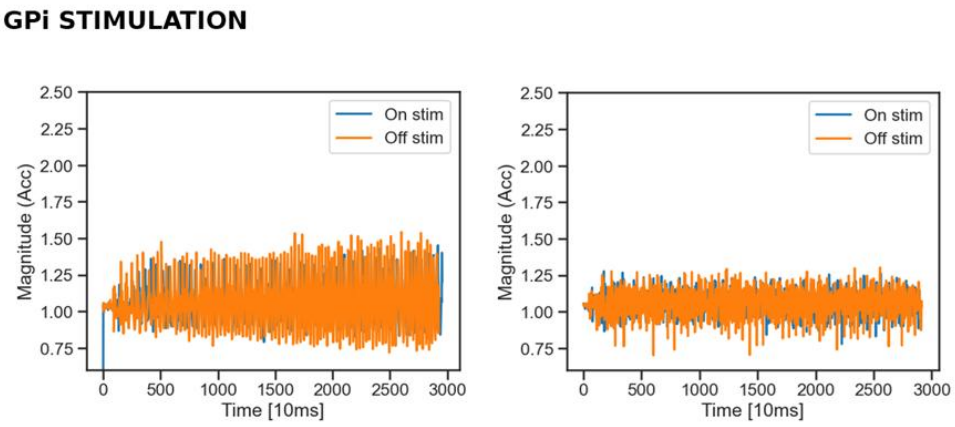


Figure 5.4 Accelerometery data for levodopa challenge (on/off medication), STN and GPi on/off stimulation. STN = Subthalamic nucleus, GPi = Globus pallidus interna.

5.4 Discussion

5.4.1 Tapping characteristics measured by levodopa challenge

The results of levodopa challenge corroborate previous findings, showing that speed of tapping improves after administration of medication (see discussion in Chapter 3). This has been extensively studied in the literature through a range of metrics similar to those used in this analysis: number of taps per second (Müller et al., 2002; Teo et al., 2013; ZhuParris et al., 2023), frequency (Akram et al., 2022; Baston et al., 2016; Broeder et al., 2023; Calandra-Buonaura et al., 2016; Hong et al., 2024), ITIs and error rate (Thijssen et al., 2022; ZhuParris et al., 2023). The rhythmicity of finger tapping has also been measured through variance (Akram et al., 2022) and standard deviation of ITI (Thijssen et al., 2022), yielding results replicated in this chapter.

Poincaré analysis has not yet been applied to finger tapping tasks, although it has been used in the assessment of gait variability in PD (Ferreira et al., 2019; Stoco-Oliveira et al., 2021; Su et al., 2023). The main advantage of its use over standard measures of variability is the ability to separate short- and long-term changes. The reduction of gait variability after administration of medication has been observed in some (Bryant et al., 2011; Schaafsma et al., 2003) but not all (Su et al., 2023) experiments. The results of present study stipulate that both short (SD1) and long-term (SD2) variability of finger tapping improve during levodopa challenge. The reduction in SD1 could be at least

partially attributed to reduction in halts and hesitations. There was a median of 6.5 short stops in the off-medication group, with many participants experiencing more than 1 longer (>1s) freezes during the task. Walking is usually assessed over a two-minute period, and contains multiple data points sampled from several IMUs, whereas finger tapping relies on a series of short signals in the 30 second window. Thus, the SD1 reduction may be less apparent when all these events are removed, or when the analysis is applied to a longer time series or to signals from the watch accelerometer data. SD2 could be considered a measure of gradual slowing or fatiguability and can similarly be influenced by dysrhythmic and involuntary movements (dyskinesias, hesitations, tremor, freezes). Interestingly, there was no discernible change in the hypothesised metrics of fatiguability (frequency differences: min/max, top and bottom quarter difference). This was also evident in similar studies (Arias et al., 2012), which concluded that finger tapping may not be a test of choice for fatigue measurement. SD2 could be used as a surrogate measure in this respect, although caution must be applied when interpreting it without considering other dysrhythmic features. Arias and colleagues also suggested that some participants may try to execute the task very fast initially, which will generate fatigue even in healthy controls. In this study, participants were asked to perform finger tapping at their own speed. Some attempted to do the task as quickly as possible, others focussed on regularity. Tremor and dyskinesias were also noticeable for some participants. This heterogeneity may have influenced the ability to identify global slowing more reliably.

The aim of examining patients through levodopa challenge during preoperative assessment is to establish medication responsiveness. Currently, a difference of 30 percent or more is considered desirable for DBS selection due to favourable post operative results (Welter et al., 2002; Zheng et al., 2021). It is difficult to directly compare normally distributed global differences in MDS-UPDRS to non-parametric features of finger tapping. A crude way of assessment could be to compare differences in medians of individual features. For example, administration of medication improved mean ITI durations by 25.8%. This should not be used in isolation, however, as MDS-UPDRS integrates features of speed, amplitude, and rhythm, and can do so on an unequal basis

(see Chapter 2). All but one of the participants included in this study were deemed appropriate for DBS, which meant that, apart from fulfilling other criteria, a satisfactory response to medication was observed. This means that, overall, the proposed set of features can detect levodopa responsiveness in this population – supporting the hypothesis of this chapter. A more intricate study could be devised, where finger tapping task could be used to examine a more diverse population, e.g. composed of balanced responders and non-responders. An agreement between digital and clinical assessment could then be examined more closely. Furthermore, finger tapping features presented in this thesis could be used to estimate the effectiveness of DBS treatment long-term, potentially laying a foundation for the use of this task in more sophisticated preoperative assessment.

5.4.2 Tapping characteristics measured in STN-DBS

DBS is an effective and established treatment for PD. The most frequently selected surgical targets for stimulation are STN or GPi, with either improving several motor symptoms such as bradykinesia, rigidity and tremor (Anderson et al., 2005; Krack et al., 1997; Limousin et al., 1998; Odekerken et al., 2013). STN is often a preferred target due to a greater reduction in medication, larger "off state" motor improvement, and less need for reoperation (Schwalb and Merker, 2016). The results of the present study replicate similar experiments where STN improved both the speed and variability of finger tapping movement, as assessed by means of frequency and standard deviation of ITI (Kim et al., 2023; Papapetropoulos et al., 2008; Taylor Tavares et al., 2005).

An improvement in ITI durations, and their frequency derivatives has a strong physiological basis. In sequential, learned motor tasks such as alternate finger tapping, the pre-supplementary motor area has been suggested to be involved in the initiation of motion sequences (Kennerley et al., 2004; Thaler et al., 1995). When the voluntary tapping movement is generated, there is an activation of functional connectivity between STN and pre-supplementary motor area, through indirect and hyper direct pathways (see Chapter 1 on detailed discussion of neurocircuitry of PD) (Jia et al., 2018). Stimulation of the STN may thus interfere with this pathway, modulating the amplitude and

frequency of finger, hand and arm movements. It has been suggested that there could be individual spots within the STN that could preferentially improve or lower the frequency of tapping (so-called "sweet" and "sour" frequency or amplitude spots), scattered across the dorsolateral and ventromedial axis of the STN (Kim et al., 2023). Sweet spots for postoperative improvement of bradykinesia have also been identified (Boutet et al., 2021; Dembek et al., 2019). Differences in lead positions within the nucleus could then result in variability in individual change effect sizes, as could be seen in Figure 5.7. This differential improvement can also be linked to the activation of separate STN-prefrontal pathways, although this is yet to be fully elucidated (Kim et al., 2023).

The improvement in finger tapping variability features is similar to those previously studied in STN-DBS gait assessments (Hausdorff et al., 2009; Su et al., 2023). The importance and neurophysiological origin of movement variability in STN-DBS has been widely studied (Su et al., 2023). Emerging evidence suggests that gait irregularity in PD transcends a purely dopaminergic origin. Beyond the well-established dopaminergic neuronal degeneration within the substantia nigra pars compacta, a concomitant loss of cholinergic neurons is observed in the pedunculopontine nucleus (PPN) (Hamani et al., 2007; Hirsch et al., 1987; Zweig et al., 1989). In animal models, postural and gait pathology can be elicited by inducing purely cholinergic lesions in PPN, without any dopaminergic loss (Karachi et al., 2010). Post-mortem studies in humans reveal a correlation between the severity of freezing and falling episodes and the extent of cholinergic neuronal loss in the PPN. This phenomenon has been used to repurpose cholinesterase inhibitor drugs, with the aim of improving gait and balance in PD patients. So far rivastigmine and donepezil have been studied in this context, with very limited success (Pagano et al., 2015), except for one study (Chung et al., 2010). Since there are reciprocal STN and PPN connections, an STN-DBS signal could improve the variability of finger tapping movement through this pathway (Ferraye et al., 2011; Stefani et al., 2007). This is of clinical interest since gait variability has been associated with falls risk (Hausdorff et al., 2001; Schaafsma et al., 2003; Yogev et al., 2005).

The improvement in all motor parameters is not universal. Some patients report subjective worsening of gait performance despite global motor benefits (van Nuenen et

al., 2008). Whilst some of these effects could be attributable to disease progression, there is certainly room for programming adjustment and troubleshooting of the stimulation system (Pozzi et al., 2022). This may mean that different trajectories of changes in features could be due to stimulator settings or lead positioning. With such a small population, it is difficult to do this with any statistical validity. To reduce heterogeneity of the sample, all participants included in the study were seen after programming, on the anniversary of their treatment, and only after any changes in medication and settings were implemented by the treating physician. It is not uncommon, however, for changes in symptoms to be discovered and reported at a later date. Thus, a true standardisation of settings would be more desirable, and could be feasible with larger populations.

5.4.3 Tapping characteristics measured in GPi-DBS

The comparison of results of GPi-DBS and STN-DBS finger tapping features reveals that these two populations have vastly distinct responses to stimulation, at least in the realm of upper body bradykinesia. None of the conventional metrics of speed and variability of hand tapping motion showed any significant difference once the stimulator was switched off, at least on a group level. A few participants showed improvement, some mild worsening, and about a third stayed the same. Whilst there are no published studies on finger tapping in GPi-DBS, clinical observations from controlled trials show that bradykinesia is only mildly improved with this surgical target (Anderson et al., 2005). This finding was further supported by a more recent NSTAPS study (Odekerken et al., 2013), although neither measured finger tapping specifically. These sparse data are not conclusive but have led to the recommendation of bilateral STN rather than GPi stimulation for improvement of slowness of movement (Williams et al., 2014). For detailed discussion of how this device could be used in selecting DBS targets, entropy analysis methodology, and statistical considerations, please refer to Appendix B.

5.4.4 Accelerometery and future directions

This chapter illustrates how many features can be derived from a simple time series of ITIs and dwelling time durations. The last section of results shows a very preliminary

dataset of accelerometer traces. Even a simple analysis of magnitude revealed significant differences in on/off states for medication and stimulation, on an individual level. A more sophisticated study of the data could focus on amplitude, missing plates, shapes of individual taps and global trends in variability and entropy of the data. New machine learning algorithms could be applied to this dataset in the future, potentially revealing important physiological traces. As is the case with all small number studies, a larger population would allow for more statistically significant findings, especially in the largely heterogeneous sample of STN-DBS and GPi-DBS participants. Larger studies could also command adequate statistical power to conduct subgroup analysis with regard to stimulation settings, lead positions, and laterality of symptoms. Whilst DBS is usually offered to Hoehn and Yahr >=2 participants (with disease affecting both sides), a signal of change could be amplified by analysing "most affected" sides only. It is important to note that this approach remains controversial (for discussion and review of studies see (Lin et al., 2021). In clinical practice, all patients are evaluated bilaterally (by comparing sums of all MDS-UPDRS scores) and have bilateral stimulators, and thus no separation was applied in this study. Finally, the collection of outcome metrics for pre-operative participants who undergo surgery could lead to interesting predictive models, informing future patient selection and surgical target choice.

A key limitation of this study was the absence of direct comparison with existing commercial devices such as smartphone applications, tablets, or keyboard-based systems. While our apparatus offered high-frequency sampling (1KHz) and precise capacitive sensing, we cannot definitively claim superior performance without head-to-head validation against these established tools. Future work could address this by conducting parallel recordings with multiple devices and analysing downsampled data from our apparatus to match the lower sampling rates of commercial alternatives (typically 60-120Hz). This would enable direct comparison of derived metrics and assessment of whether the higher sampling rate provides meaningful clinical advantages. Such validation would be particularly valuable for determining if the additional complexity and cost of a dedicated device is justified compared to more readily available consumer technology.

5.4.5 How were patients involved in this study?

The apparatus would not achieve its improvements without invaluable feedback from participants, their families, and carers. The early patient involvement in the design and testing of the devices was pivotal, as the shape of the 3D models for the base and watch as well as task protocol were discussed. The main points raised by the participants are as follows. A quick (under 30 seconds) setup of the finger tapping task was praised, especially given that any extension of the vulnerable off medication / off stimulation state is associated with significant discomfort. A few participants contrasted this with other studies they had participated in, where equipment setup could take up to 5-10 minutes. Patients also expressed appreciation of the digital finger tapping assessment, praising its objectivity and subjective scientific validity, especially compared to tapping in between coloured tape on the table. A statement was frequently made that this task does not add any extra burden, as finger tapping is assessed clinically anyway.

The main points of engineering feedback included a suggestion of a more robust case design, as the initial model's screws loosened over time, causing the tapper plates to slide—a detail the participants found unsatisfactory. To address this, the case was reinforced, and the rubber feet were enlarged to enhance stability and comfort. Additionally, participants suggested improvements to the watch straps, advocating for elastic and Velcro-based designs for ease of use. They were open to performing the task at home, provided they received proper instruction. Suggestions also extended to the user interface of a potential data collection app for home studies, emphasizing the need for an intuitive and patient-friendly design.

This chapter would be impossible without the three specialist nurses working within the neuromodulation team – Beth Petic, Claire Fletcher, and Laura Baccini. They have taken time out of their busy clinical schedules to screen patients, allow extra time in their clinics for research and extended countless hours of patience and understanding toward developing this task. Their short but precise feedback on the construction and analysis of the finger tapping feature helped shape the final product discussed in this thesis.

5.5 Conclusions

This analysis presents preliminary results of a validation study of a novel finger tapping apparatus comprising two plate sensors and a wearable watch IMU sensor. The system generated hyper-accurate (1kHz) raw data sets that are easily interpretable by data analysis packages. The study's findings indicate that the system is capable of capturing nuanced motor deficits masked by levodopa administration and can be a valuable tool for assessing the efficacy of STN and GPi stimulation on upper body bradykinesia.

For participants undergoing the preoperative assessment, the administration of levodopa significantly improved the speed of finger tapping, as evidenced by shorter ITIs and increased taps per second. There was also a notable improvement in the rhythmicity of tapping post-medication. Postoperatively, patients with STN-DBS showed improvements in speed, rhythm and both short- and long-term variability, when the stimulator was on, compared to the off state. In contrast, patients with GPi-DBS did not exhibit changes in the bradykinetic features produced by the apparatus. These results suggest that STN DBS may be more effective than GPi DBS for alleviating bradykinesia in PD patients, aligning with the current preference for STN as a surgical target for DBS in PD.

6

Discussion

This thesis presents an analysis of bradykinesia in PD, utilising digital sensors and machine learning to improve the assessment of symptoms and prediction of fall risk. It also introduces a novel measurement device for a more precise assessment of upper body bradykinesia.

Chapter 2 presented the evaluation of commercially available sensors and compared their performance against an MDS-certified clinicians' assessment of finger tapping, hand movement, and pronation supination. The results showed a high congruence between clinical scores and sensor estimates, suggesting that a single-finger accelerometer and gyroscope could enhance the monitoring of upper body bradykinesia in PD. Differential contributions of speed, amplitude and rhythm were also examined and integrated into the assessment using machine learning algorithms. Future studies should focus on the integration of these sensors into routine clinical practice, examining their long-term reliability and patient adherence. The ability of these sensors to reliably automate MDS-UPDRS assessment could also be utilised in home monitoring, telemedicine, and continuous, passive monitoring studies.

There is a significant potential for these sensors to improve the clinical management of PD through more personalised and responsive treatment plans. This was further elucidated in Chapter 3, which focused on the assessment of response to antiparkinsonian medication. The findings of this chapter demonstrated that a single-finger sensor, coupled with body-worn IMUs, can reliably measure the response to the first administration of antiparkinsonian medication in de-novo patients. The data suggest that, upon commencement of medical therapy, a flattening of progression could be observed in patients' motor functions. This aligns with previous clinical observations. Masking of progression signals indicated which features may not be useful in tracing the disease in

longitudinal studies of patients already established on medication. Future analyses could focus on following up the de-novo patients after the introduction of medication. Longer follow-up could establish whether the masking of these features is less pronounced later in the disease. The time points when these features become important for disease monitoring could also be established.

Sensor data analysed by machine learning algorithms could also help predict important clinical outcomes such as first falls in PD. This was explored in Chapter 4. The findings suggested that machine learning models trained on kinematic data successfully calculated the likelihood of experiencing the first fall in 24- and 60-months follow-up. The feature selection identified several variables that could influence the risk of falls. Lower mean stride length was associated with a higher risk of falling, potentially due to a compensatory mechanism aiming at improving dynamic balance whilst walking. The short, shuffling gait is frequently observed in PD clinically, especially at later stages of the disease. This metric is thus expected to deteriorate with disease progression. The remainder of gait parameters measured the variability of walking. The association between disruptions in coordination and falls have been widely studied in the past. This study provides further evidence that such pathology could be objectively measured and analysed by machine learning models. The predictive capability of these models is crucial for proactive patient care and fall prevention strategies. For example, resource-intensive fall prevention programmes could be offered to people who are of the highest risk, thus maximising the clinical efficacy of the intervention. Future research could focus on refining the models to increase their predictive accuracy and exploring their application in real-world settings, such as at-home monitoring systems, movement disorder clinics or primary care. Large datasets could be used to that end, for example through the analysis of accelerometer data from the UK Biobank.

Chapter 5 presented a novel device designed for finger tapping measurement, paired with bespoke analytical software. The data sourced from these devices showed potential in assessing clinically observable characteristics of bradykinesia. The finger tapping device was able to successfully detect differences between ON/OFF medication states and ON/OFF DBS stimulation states. For levodopa challenge, measures of variability of

tapping proved to be the most useful in distinguishing between the two states. The Poincaré analysis showed that both short term (SD1) and long term (SD2) variability of intervals was improved after administration of antiparkinsonian medication. Medicated patients' assessment was also characterised by fewer errors and hesitations (both short stops and longer time freezes). The magnitude of accelerometery-measured movements also increased after the reintroduction of medication, which suggests an improvement in the amplitude of movement – an expected finding in this population. Examination of levodopa responsiveness is an integral part of the preoperative assessment of patients for DBS surgery. The variability, error, hesitation and range of movement metrics proposed by this thesis could be used in the future for an objective selection of patients. The characteristics of tapping in the DBS population varied depending on the surgical target. In the STN-DBS population, there was an improvement in interval duration and variability metrics in the ON stimulation condition. These changes were not apparent in GPi-DBS, suggesting that GPi stimulation may not produce as profound of a change on upper body bradykinesia. Other explanations such as heterogeneity of the sample and lead placements were also discussed. Overall, the results support the notion that the finger-tapping device could be a viable assessment tool for a post-operative evaluation of patients with DBS implants. Ongoing development should aim to enhance the device's precision and explore its use in other movement disorders. Accelerometer and gyroscope data could also be further analysed through time series algorithms or by cutting the stream of data into distinct taps and analysing the waveform created by the sensor trace. This could provide another level of precision in how the tap is performed, potentially giving a more granular assessment of the amplitude, rigidity and rhythmicity of movements. Collaborative efforts with technology developers could lead to more accessible and user-friendly designs.

7

Appendix A – TRIPOD AI Checklist For Risk Prediction Reporting



Version: 11-January-2024

This checklist refers to the development of risk prediction model from Chapter 4

Section	Checklist item	Reporting
Title	Identify the study as developing or evaluating the performance of a multivariable prediction model, the target population, and the outcome to be predicted	We use a multivariable prediction model with patients with PD as target population and outcome to be predicted as falls
Introduction	Healthcare context and rationale	Falls are an important clinical outcome. We use a prognostic model to evaluate whether baseline, sensor-derived gait characteristics as well as clinicodemographic variables can help predict risk of falls within up to five years of recruitment.
	Describe target population	Intended purpose of the prediction model is to be used to develop care pathways based on stratification of falls risk.
	Describe any health inequalities between sociodemographic groups	Age was the only clinicodemographic variable that was significantly different between fallers and non-fallers. However, the model evaluation did not include other sociodemographic variables such as ethnic background, education, income bracket or post code.
	Study objectives	The study describes a development of a prediction model
Methods	Data sources	The data was derived from the OxQUIP study, a longitudinal observational study. The rationale for using it was that the baseline sensor data was available for all participants and that the study was conducted long enough to allow for up to five years of follow-up.
	Dates of data collection	Baseline sensor data was collected at the first visit. The flowchart in Fig. 1 outlines at which point fall indices were recorded.

	Key elements of study settings	Data collection was carried out at the John Radcliffe Hospital in Oxford, in a research clinic. Fall indices were recorded through clinical history taking, telephone follow-ups and, whenever possible, confirmed through hospital and GP records.
	Eligibility criteria	Exclusion and inclusion criteria are listed in methods section.
	Treatments received	This was a purely observational study.
	Data processing	Full explanation of data processing, extraction, and feature selection is listed in methods.
	Outcome and time horizon	The assessed outcome was occurrence of the first fall, participants were surveyed for up to five years.
	Blind assessment of the outcome to be predicted	There was no blinding of outcome measurement due to the nature of outcome variable.
	Describe the choice of initial predictors	Literature search, as outlined in the introduction section (see literature table).
	Clearly define all predictors	One predictor, existence of a fall.
	Predictor subjective interpretation	A fall, similarly to previous studies (Allen et al., 2013; Araújo et al., 2023; Vitorio et al., 2023), was defined as an unintentional event that results in a loss of balance and subsequent complete coming to the ground or some lower level, not due to a major intrinsic event or overwhelming hazard.
	Study size	See figure 1 for the full explanation of how the study population was selected.
	Missing data	All participants had their baseline sensor data collected. A few were lost to follow-up (see Fig.1), and these were excluded from analysis.
	Data processing	Full analytical pipeline is reported in methods section. Specific references are made to rescaling, standardisation, avoidance of data leakage, etc.
	Model performance evaluation	Metrics of model evaluation and the rationale for their use is presented in methods section.
	Model updating	No model updating was used in this study.
	Class imbalance	Class imbalance methods (incl. downsampling) are presented in the methods section.
	Model fairness	No specific methods were used to assess model fairness.
	Prediction output	Classification models were used with parameters and types of models outlined in the methods section.
	Development and evaluation	Cross validation and confusion matrix methodology is explained in methods section. Due to scarcity of the data there was no validation set used.
Open science	Funding	Sources of funding are clearly indicated in the first chapter.
	Conflicts of interest	My supervisors (J.J.F. and C.A.A.) were supported by the National Institute for Health and Care Research (NIHR) Oxford Biomedical Research Centre (BRC) J.J.F. has received consulting fees from Abbott and Medtronic, unrelated to this study. J.J.F. and C.A.A. have received research grant support from UCB Pharma. The remaining authors declare no competing interests.

	Protocol	The study protocol is outlined in Chapter 1 and 2.
	Registration	OxQUIP study was registered (IRAS ID 211382)
	Data sharing	Data can be shared upon reasonable request
	Code sharing	Code has been made available on public repository
Patient and public involvement	PPI	Details on how patients were involved in the study are presented in section 4.4.4.
Results	Flow of participants	Full flowchart is presented in Fig. 1.
	Patient characteristics	Clinicodemographic characteristics are presented in Table 4.2.
	Important predictors	This can be seen in Table 4.3.
	Number of participants with outcome events at each stage	Full flowchart is presented in Fig. 1.
	Provide details of prediction model code	This is available in public repository https://github.com/OxQUIP-Study/FallRiskPD
	Reporting of model performance estimates	ROC curves are presented in Fig. 4.4
	If examined, report examination of heterogeneity in model performance across key subgroups	This was not examined.
	Report results from model updating	Model updating was not performed.
Discussion	Overall interpretation of the main results	This is summarised in discussion, with direct comparisons to similar studies in the field.
	Discuss limitations	See section 4.4.3.
	Discuss how poor quality of unavailable input data should be assessed when implementing prediction model.	The model was derived from six body-worn sensors. It is preferrable that similar system is used in the future. However, the most significant features used as predictors in this model could be derived from lumbar and foot sensors only. Thus, good quality data from these sensors should be prioritized in future studies.
	Specify whether users will be required to interact in the handling of the input data.	The sensor data extraction is done automatically using Opal's APDM system.
	Discuss next steps and future research	See section 4.4.4.

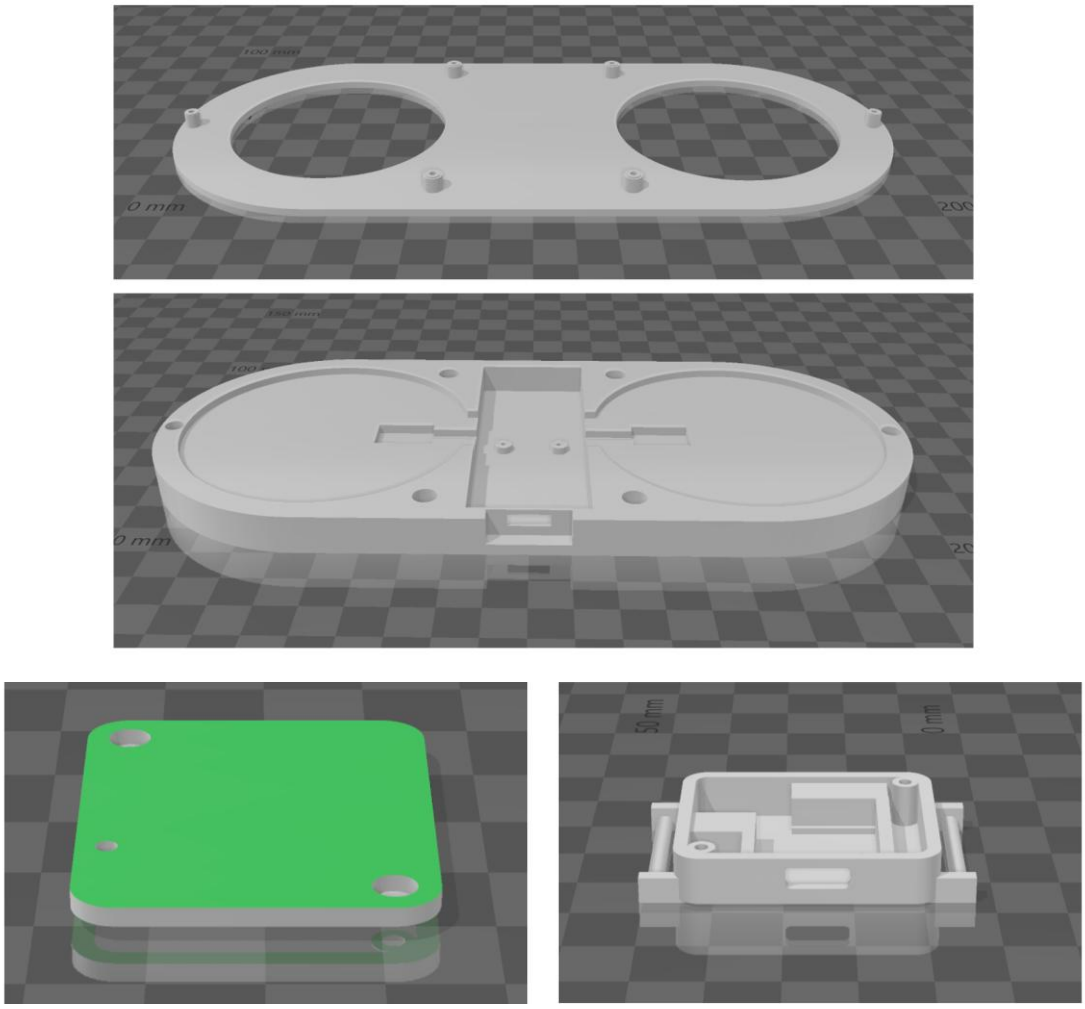
8

Appendix B – Engineering, Data Extraction Pipelines, and Entropy Analysis of the Upper Body Bradykinesia Apparatus

Methods – apparatus

Tapping plate hardware

The tapping apparatus consisted of two circular stainless steel metal plates of 60 mm diameter each, separated by 30 mm. Two metal springs were laid underneath the plates to ensure continuous connection and durability under varying pressures exerted by the finger tapping. The wires were connected to the microcontroller as described below. The electronic parts were encased in a custom-made 3D printed case (see below). The model was printed on a Prusa MK3S 3D printer using RS PRO 1.75mm PLA 3D filament (RS components). Four rubber feet (3M materials) were affixed to the lower panel to ensure stability. Power was supplied through micro-USB wire, which also acted as a primary source of data streaming.

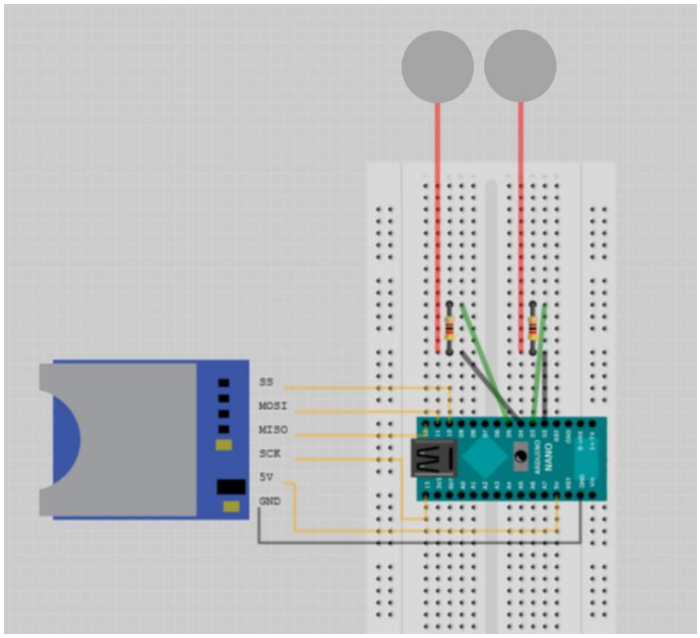


Rendering of 3D models of tapping device (upper panel) and watch (lower panel). Each panel represents top and base pieces, which are printed as separate parts and affixed by screws after electronic part assembly.

Capacitive sensing

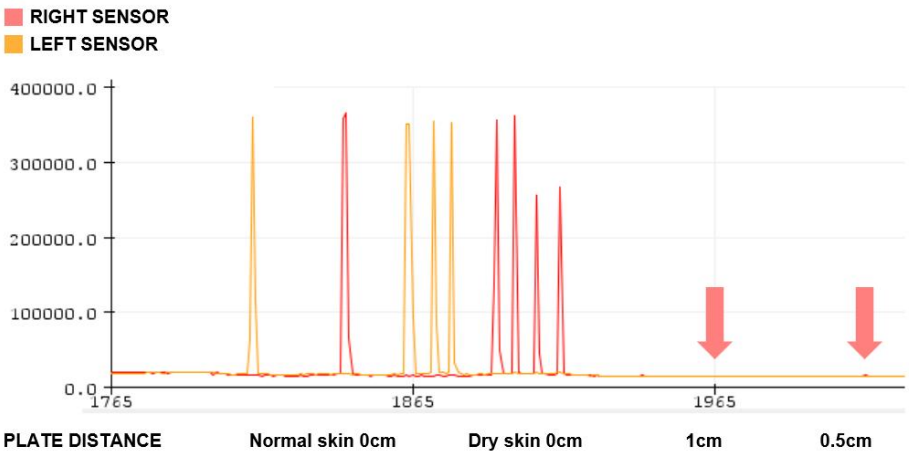
The finger touch sensation was detected as follows. Two circular metal plates acted as capacitors, each storing electrical charge (see below). Upon approximation of a human finger, a plate becomes rapidly charged through capacitive coupling, and when the finger leaves the plate, the capacitor is discharged. The microcontroller then measures this change of capacitance through two pins, connected via a metal spring pressing against the plate. This is done through launching of a 5V signal on one pin and measurement of voltage on another pin, with the capacitor in between. A counter is started to measure the time it takes for input voltage to match output voltage (in arbitrary units). A contact with human skin generates a spike in this number to a certain threshold, which can then

be used to determine that a touch has taken place. For stabilisation of the circuit, the send pin was connected through a 10 megaohm resistor.



Schematic of the microcontroller (Arduino Nano) with two metal plates acting as capacitive touch sensors. Micro USB provides 5V power and acts as a primary data transmission tool. A backup of all experiment recordings is stored on a micro-SD card. The resistors are 10 mega Ohm each.

Most human skin contacts for stainless steel plate generate signals of >22x background noise magnitude. To avoid under-detection of touch, for example due to dry and fragile skin, a threshold for actual touch was set at >3x background noise. Since the entire detection is based on an adaptive capacitance change threshold, little to no pressure is required to operate this apparatus. This offers a unique advantage over keyboards and button-based systems, which may be particularly challenging to use in frail and late-stage disease population. As seen in the calibration tape, the device was still able to distinguish real touch from a <1cm finger approximation (see below). Upon every launch, the microcontroller samples background noise and calibrates the detection curves, so that thresholds for touch can be dynamically deployed across different climate settings. A small application can also be uploaded to the microcontroller to check and plot individual values, for validation and troubleshooting.



Establishing thresholds for detection of touch with respect of capacitive sensor values for normal and dry skin touch (0cm), and finger approximation (but no actual touch) at 0.5 and 1cm.

Wrist sensor hardware

To measure the upper limb motion in between tapping events, a wearable accelerometer and gyroscope sensor were needed. This unit was designed using a XIAO nrf52840 microcontroller, which was encapsulated in a 3D printed plastic case resembling a watch. The case was printed using the same filament and printer as the stationary metal plate case. Two Velcro straps were attached to the handles of the case, to allow for safe and comfortable affixation of the unit to the participant's wrist. For the purpose of the initial validation trial, the power was supplied through micro-USB wire. The same micro-USB wire was used to stream data to the processing unit. This was done to reduce potential points of failure and to allow live troubleshooting. The unit is equipped with Bluetooth Low Energy (BLE) system that is paired with the microcontroller housed in the tapping device base. Data stream can be broadcast into the base microcontroller via BLE and either saved to local SD card or further streamed to the receiving computer via micro-USB wire. The unit also has a functioning charging chip, which enables its battery powered use. A space for micro battery unit has been allocated in the plastic case.

XIAO nrf52840 is a multi-purpose chip with a few sensors that could be utilised in IMU devices. Of interest are the accelerometer and gyroscope sensors housed on the board

in a LSM6DS3 system. The LSM6DS3 unit is a system-in-package that contains a digital accelerometer, a digital gyroscope and a temperature sensor with a 4 kbyte buffer for data batching. The digital accelerometer measured the acceleration of the board along the X, Y, and Z axes, in units of g (9.81 m/s^2) ± 4g, and a sensitivity of 0.122 mg per least significant bit (LSB). The digital gyroscope measured the angular velocity of the board around the X, Y, and Z axes with range set at ± 2000 degrees per second (dps), and a sensitivity of 70 mdps/LSB.

The sampling rate of the sensors was set to a default of 104Hz. This can be potentially increased up to 1666 Hz by overclocking the Inter-Integrated Circuit (I2C) bus, which collected the synchronised data from both sensors. Here, the I2C protocol worked as follows. The circuit utilised two wires: SDA (Serial Data) and SCL (Serial Clock). The SDA line carried the data bits, and the SCL line provided the clock signal to synchronize the data transfer. Upon commencement of the protocol, the master device initiated the communication by sending the address of the slave device (selected sensor with unique address), followed by a read or write bit. The slave device responded with an ACK (acknowledge) bit if the address matches, or a NACK (not acknowledge) bit if it does not. Then, the master and the slave exchange data frames, each followed by an ACK or NACK bit. The communication ended with a stop condition.

A wholly assembled system is visible on the photograph below. For the pilot study presented in this thesis, both units (tapper and watch) were directly connected to the receiving computer. This was done to minimise points of failure with power supply and data transfer being done through a stable USB connection. A ready-for-production apparatus could be capable of complete wireless operation.



Photograph of a fully assembled apparatus (tapping base and watch). Both are connected to the same receiving computer, which provides power supply and data transfer.

Data capturing software

The microcontroller read values of both sensors every millisecond (1KHz) using a modified capacitive sensor library for capacitive finger tapping sensing (Stoffregen, 2022) and Arduino_LSM6DS3 library for accelerometer and gyroscope data. To ensure synchronisation of the data streams, the signal was timestamped using the base tapper CPU clock and broadcast through the standard output. Here, the standard output stream was monitored through a micro-USB receiver, utilizing the data analysing and reporting software discussed below. A redundancy system was employed to prevent data loss. Duplicate datasets were saved on the SD card and as a raw stream file on the receiving computer. Codes for both microcontrollers (base tapper and wearable wrist sensors) were written in C++.

Data analysis and reporting software

A bespoke analytical and data acquisition package was written in Python 3.9 to handle signal processing and analysis. It contained three modules for data acquisition, single file, and mass data analysis. Once processed, the data was output in a comma separated value (CSV) file with values of plate side (left or right), time spent dwelling on the plate and inter tap interval (ITI) in milliseconds. The ITI was measured from the commencement of a tap to the commencement of a subsequent tap, and thus included the dwell time of the tap and time spent travelling in between plates. This formatting ensured backwards compatibility with other commercially available formats (e.g., OBER, iPhone apps) and meant that the analytical methods discussed below could be used on existing datasets.

Task and protocol

The tapping sensor is versatile and could be used for a variety of tasks, e.g. single index finger reaction times, one plate two thumb alternate tapping, or alternate finger tapping. Here, a simple alternate plate finger tapping task was chosen. The participants were instructed to tap on the sensor with an index finger and then to move to the opposite sensor and tap again, repeating the movement for 30 seconds. The task was selected because it offers an insight into both distal (finger flexor/extensor) and proximal (shoulder rotation/biceps & triceps) bradykinesia, with a precision-accuracy element of having to target the plate quickly but without missing. A simple cognitive attention and execution component is also present, as there is a need to remember to keep alternating between plates throughout the task. The clinical validity of alternate finger tapping task is further supported by the *in vivo* correlation of finger tapping characteristics with the substantia nigra neuronal loss studied through [18F]-6-Fluoro-L-DOPA (6-FD) PET scan (Pal et al., 2001).

Methods – feature engineering

Simple statistical descriptors of finger tapping

The following features were computed for both time dwelling on the plate and Inter Tap Interval (ITI):

- mean,
- standard deviation,
- tap-to-ITI ratio.

The following features were computed considering the number of taps and plate selection:

- number of taps per second (number of taps / 30),
- number of longer (>1 s) stops or freezes,
- error rate (percentage of taps where incorrect plate was selected, without alternation),

Variability metrics

Subsequent analysis focussed on the variability of the data. A Poincaré analysis was employed, where individual values were plotted against the one before (Hsu et al., 2012). The deviation from the line of identity in the short-term (tap-to-tap variability) was quantified using SD1, and the spread of tapping times along the identity line quantified the long-term (start of task to end of task) variability using SD2 (see below). Ratios and ellipse area formed by the two were also calculated such that:

- Short term variability $SD1 = \sqrt{\frac{\sum((x-y)-(\overline{x-y}))^2}{2n}}$
- Long term variability $SD2 = \sqrt{\frac{\sum((x+y)-(\overline{x+y}))^2}{2n}}$
- SD radio = SD1 / SD2
- Ellipse area = $\pi \times SD1 \times SD2$

The short-term variability could also be illustrated as percentage change in latencies of adjacent taps (Fig. 5.5C). A perfectly consistent individual would produce a flat line around 0 value. In less consistent individuals, different patterns of irregularity could be visualised. Autocorrelation was another measure of consistency. This statistic splits the signal into two identical time series. with one shifted in phase with the other by n lags. It then calculates the correlation between the two. The first n=0 lag correlation is always perfect (coefficient of 1) and if the series is perfectly consistent the subsequent lags 1,2,3... should be as close to 1 as possible. These values can also be transformed into the frequency domain, which was helpful in characterising fatigue as global decline in frequency, best illustrated with a rolling average. Skewness and kurtosis were also calculated as metrics of assessment of the distribution of ITI histograms.

The following features were computed to quantify the characteristics of the style and consistency of tapping:

- Tap-to-tap change mean (i.e. mean of differences between two adjacent taps),
- Tap-to-tap change standard deviation,
- Frequency mean,
- Frequency standard deviation,
- Dominant frequency,

And specifically for fatigue:

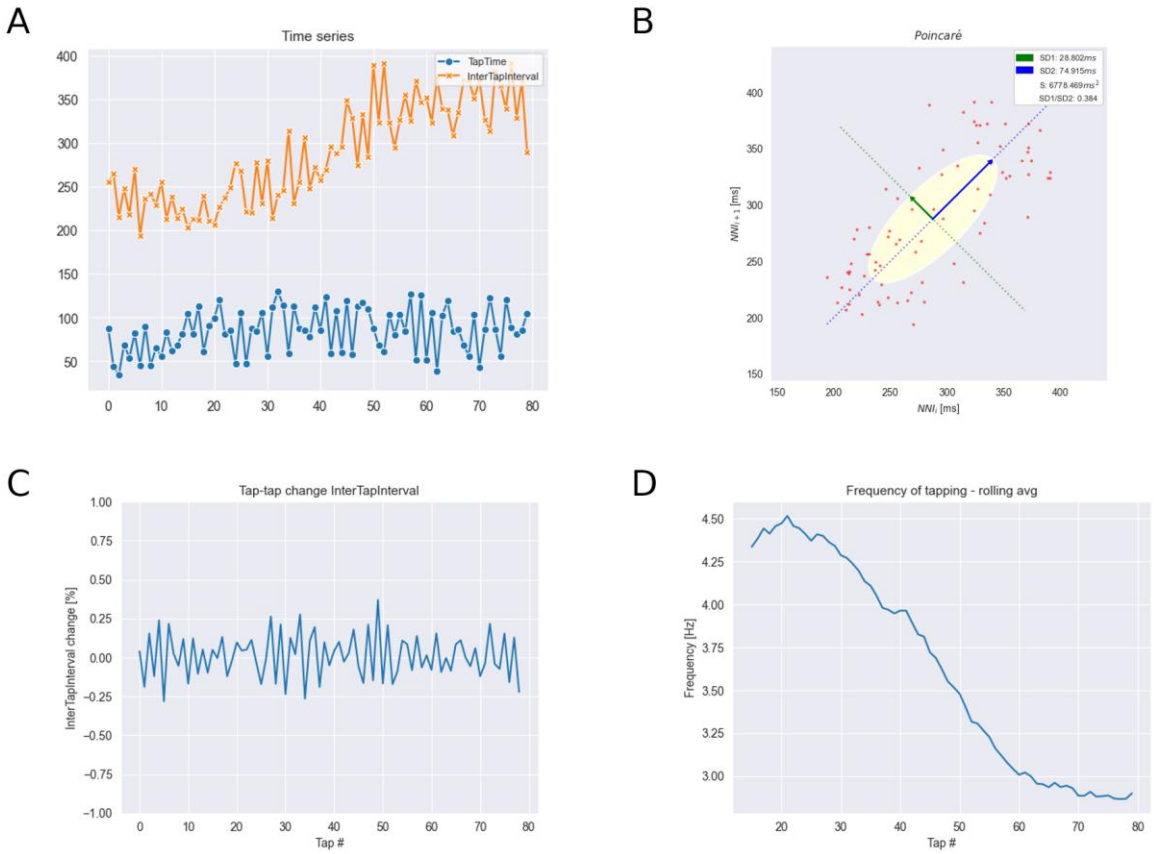
- Difference in frequencies between first and last quartile,
- Difference between minimum and maximum frequencies,

Finally, the algorithm can detect hesitations, which were peaks of latencies not long enough to qualify as a longer stop or a freeze (i.e. shorter than 1s). The program detected it using a peak finder algorithm commonly used in signal processing (SciiPy Community, 2022).

The hesitations were further characterised by:

- Hesitations number,

- Mean time of hesitation,
- Total time of all hesitations,
- Difference in number of hesitations in the first and last quartile.



Example of finger tapping readings of a participant in OFF DBS stimulation state. (A) Time series of Inter Tap Intervals and Tap Times (time spent dwelling on the plate) in milliseconds. (B) Poincaré analysis showing significant long-term (SD2) variability but normal short-term (SD1) variability, which is further confirmed on a graph (C) displaying percentage change of adjacent Inter Tap Intervals. A perfectly consistent person would produce a flat line around 0 mark, indicating no change. (D) Graph of Inter Tap Intervals transformed to frequency domain, rolling average over 7 data points. Global changes in this graph indicate progressive slowing (fatiguability) towards the end of the task, as frequency decreases. DBS = Deep Brain Stimulation.

Entropy analysis

Another common method of quantifying the regularity of signal is use of non-linear methods such as Sample (SampEn) or Approximate entropy (ApEn). These algorithms can be used to quantify the randomness of data without any assumptions about the origin or nature of the data stream, which enables a wide applicability across different research

applications (Delgado-Bonal and Marshak, 2019). Entropy measures are especially useful where classical metrics of randomness (standard deviation, skewness, kurtosis, etc.) encounter significant limitations. For example, flipping a completely random coin could produce the following series: 0,1,0,1,1,0,1,1,1. A comparable series of 0,1,0,1,0,1,0,1 could have the same or similar variability metrics, yet its regularity (alternating ones and zeros) is readily visible. This could be further quantified by evaluating whether a stream of data can be presented more simplistically, with the use of repetitive or regular terms. From the previous example, a "regular" series could be stored as: four times "01", whereas the first series cannot. Using a telegram analogy from Delgado-Bonal and Marshak's paper, a more random data series would cost more to send than a more regular one, since the latter could be expressed by repetitive patterns, thus costing less when fee is levied per word. A more modern analogy would be that of a data storage and transfer fees. Entropy algorithms aim to find such regularities and quantify randomness based on different patterns and repetitions. The mathematical framework for such calculation has been borrowed from chaos theory, thus laying the foundation for ApEn, i.e. degree of chaos and system complexity (Pincus, 1991). A low ApEn system is very consistent, predictable, and repetitive throughout the series. In finger tapping analysis, this could mean that it would be very easy to predict the next 10 seconds of ITI durations, based on already collected 30 seconds. Conversely, a high ApEn data series is highly varied, with multiple series of ITI durations and tapping patterns that are independent of each other. The algorithm accepts two terms: m (comparison window) and r (noise filter). In this analysis, the m was set as 2 in this analysis, since there are two plates to tap between, and r to 3, which represents 0.1 of the standard deviation of the dataset, as widely recommended (Yentes et al., 2013). The main limitation of ApEn is its lack of internal consistency, as evidenced by sensitivity to change in m and r parameters and length of the series (Richman and Moorman, 2000; Yentes et al., 2013). SampEn was proposed as a more stable parameter that can be directly compared between datasets (Richman and Moorman, 2000).

Both ApEn and SampEn have been extensively used in physiological research (Castiglioni et al., 2013; Montesinos et al., 2018; Yentes et al., 2018); for a comprehensive

review of the use of these and related measures in PD, stroke, ataxia and Huntington's disease see (Vanmechelen et al., 2023). SampEn of wearable sensor signals can distinguish PD from healthy controls (Coates et al., 2020), quantify postural control (Pantall et al., 2018) and assess the complexity of walking in falling and non-falling PD populations (Ihlen et al., 2018). Despite the abundance of finger tapping data, only few experiments focussed on entropy metrics. Entropy analysis of the angular velocity of a single finger sensor in the finger tapping device distinguished PD patients from healthy controls (Li et al., 2020; Shima et al., 2009), was correlated with loss of focus during the task (Groot et al., 2022), and could be used to characterize tremor (Meigal et al., 2012).

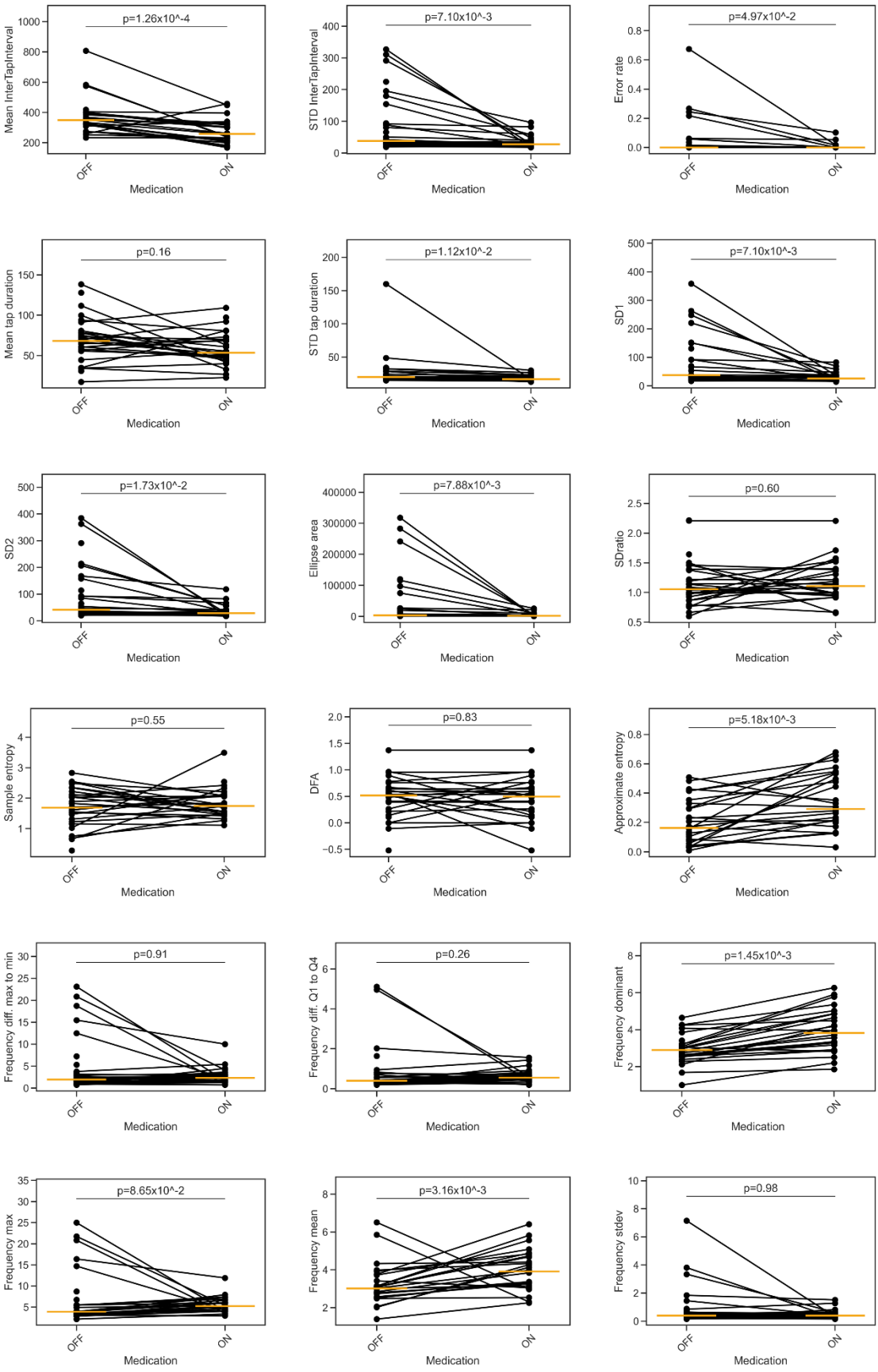
Detrended fluctuation analysis (DFA) is another way of non-linear analysis of regularity (Peng et al., 1994). In contrast with approximate and sample entropies, it focuses on long term correlations of the data. The resultant metric, called the Hurst exponent, represents the degree of long term repetitiveness ("memory") of the series (Bryce and Sprague, 2012). The exponent can be interpreted as follows: $H > 0.5$ is a "persistent behaviour" (large fluctuations followed by larger or smaller fluctuations), $H = 0.5$ a "random behaviour" (no long-range correlations), $H < 0.5$: "anti-persistent" behaviour (large fluctuations followed by smaller fluctuations of the opposite direction) – as per definition in (Likens et al., 2023).

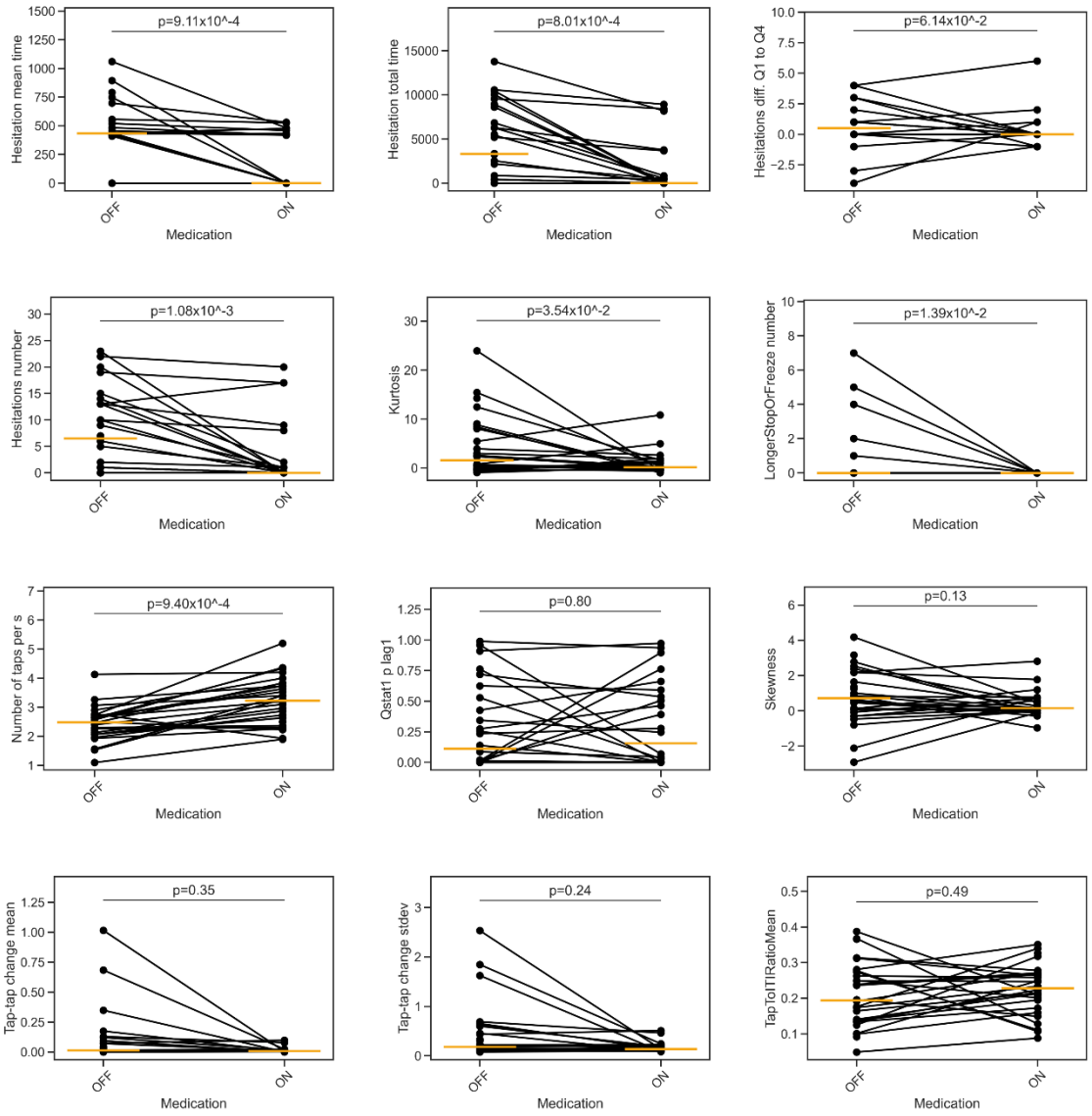
Accelerometer and gyroscope data

Data from the IMU watch sensor provide a rich and granular characteristic of movement in between the plates during finger tapping exercise. To fully analyse the complexity of such streams would escape the remit of this thesis. However, a small exploratory analysis was conducted on a sub sample of the population, where full IMU data was available. The following data processing protocol was employed. To reduce dimensionality of three-dimensional streams a metric of magnitude was be calculated as (where aX, aY and aZ are accelerometer data for X, Y, and Z axis):

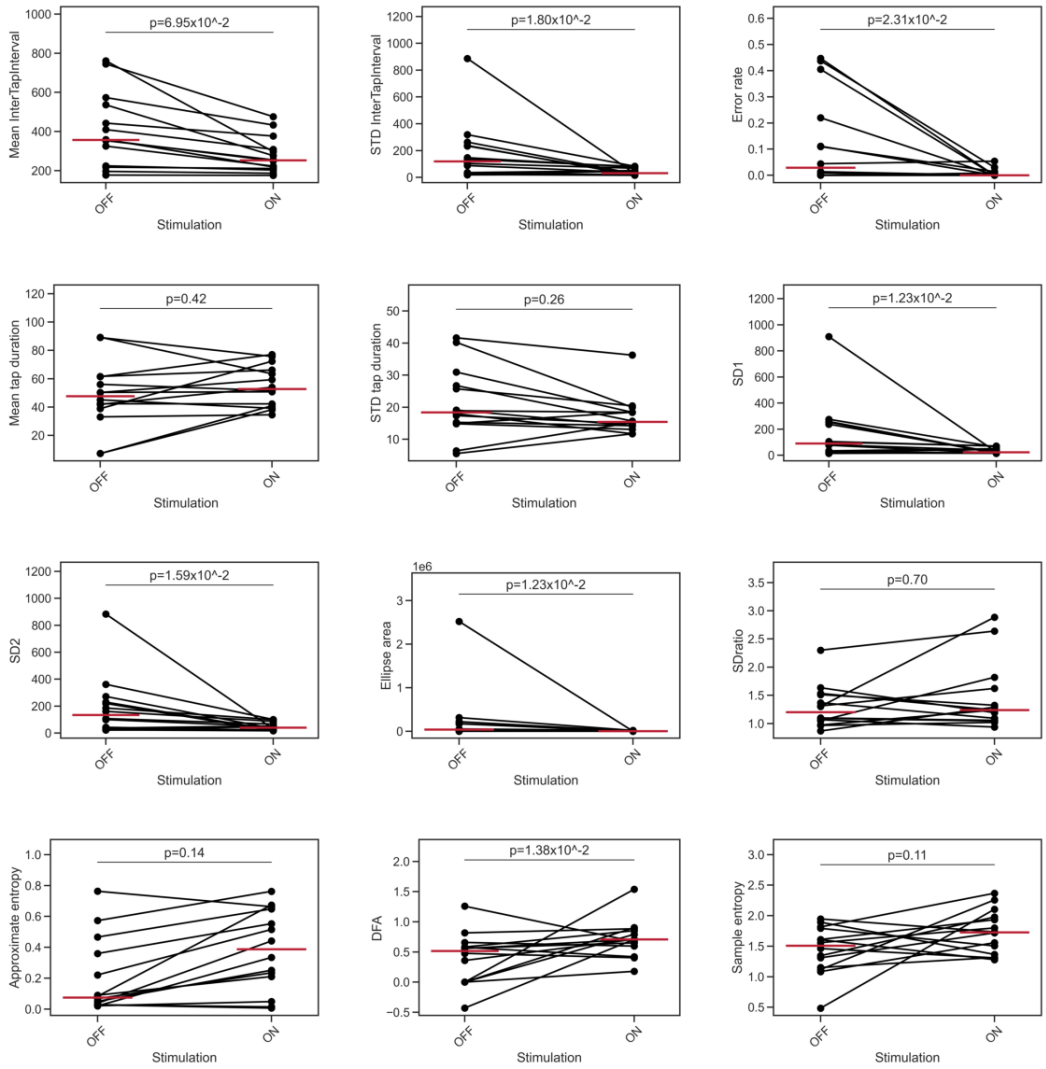
$$\text{Magnitude} = \text{sqrt}\ (aX^2 + aY^2 + aZ^2)$$

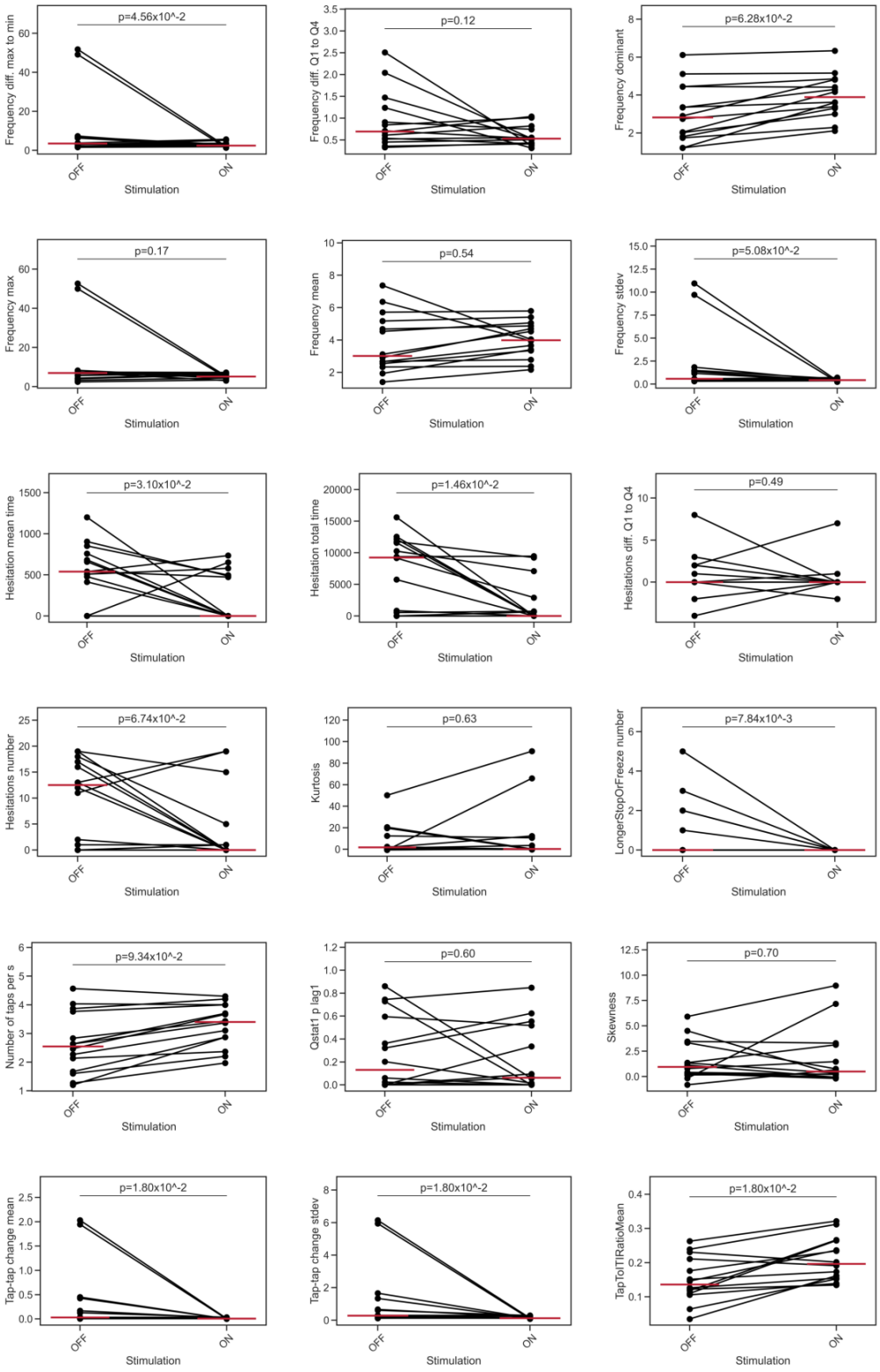
This allowed for attenuation of positional variability and allowed for a more meaningful comparison between data streams. The time series could then be visualised graphically to appreciate any changes in amplitude of the waves generated by upper body movement.


p=1.26x10^-4
Mean InterTapInterval
p=7.10x10^-3
STD InterTapInterval
p=4.97x10^-2
Error rate
p=0.16
Mean tap duration
p=1.12x10^-2
STD tap duration
p=7.10x10^-3
SD1
p=1.73x10^-2
SD2
p=7.88x10^-3
Ellipse area
p=0.60
SDratio
p=0.55
Sample entropy
p=0.83
DFA
p=5.18x10^-3
Approximate entropy
p=0.91
Frequency diff. max to min
p=0.26
Frequency diff. Q1 to Q4
p=1.45x10^-3
Frequency dominant
p=8.65x10^-2
Frequency max
p=3.16x10^-3
Frequency mean
p=0.98
Frequency stdev
OFF
ON
Medication

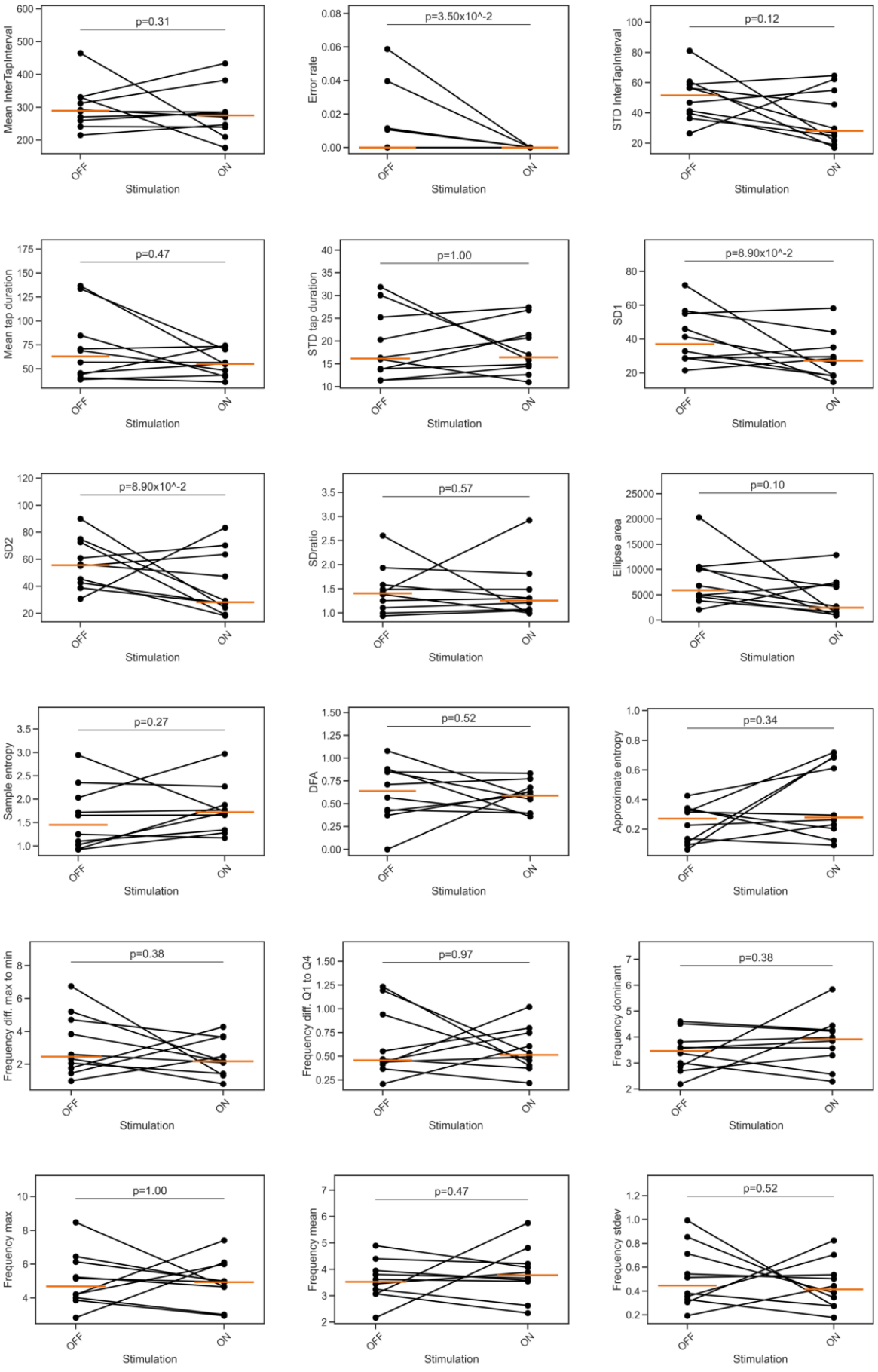


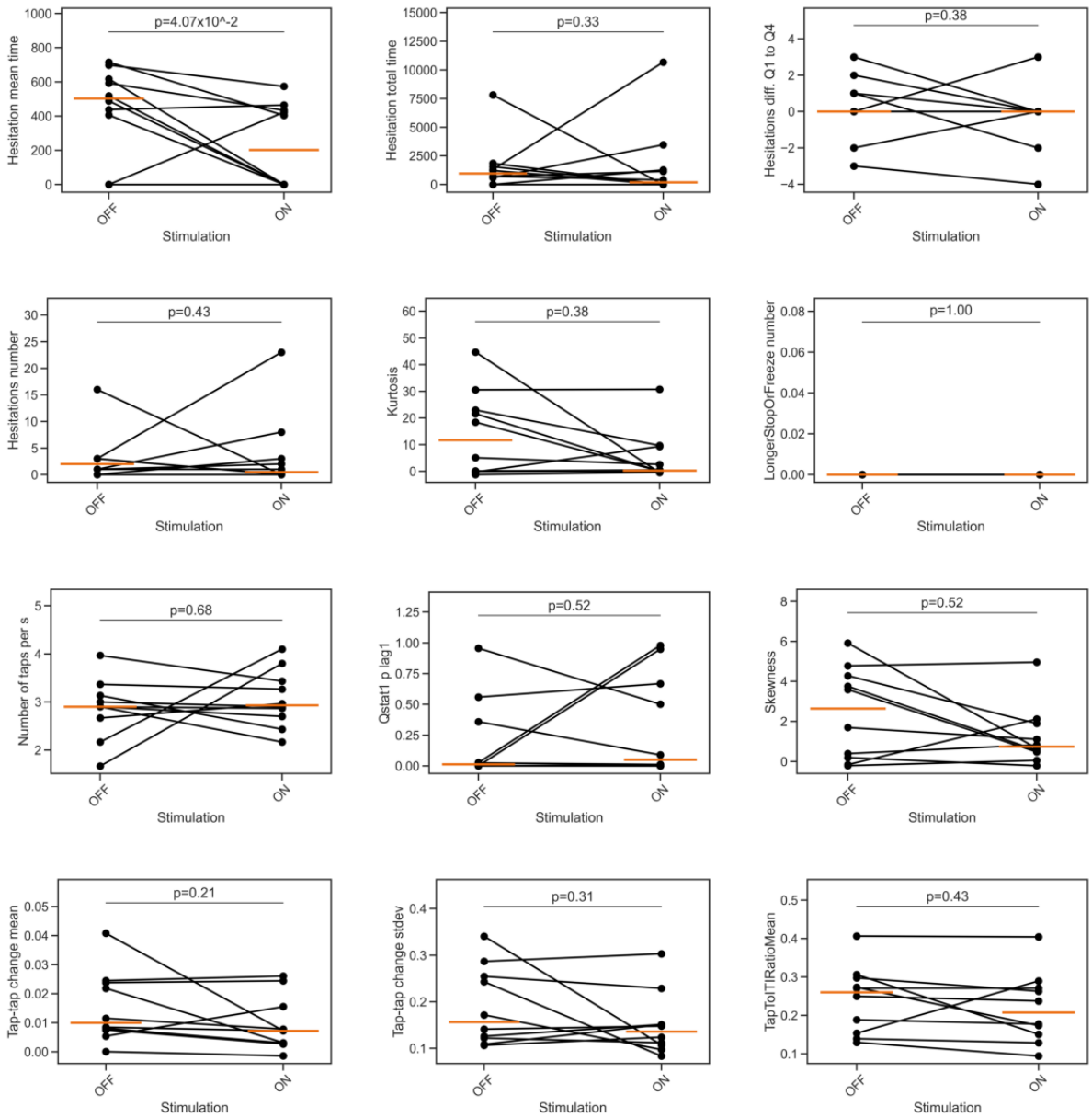
Changes in finger tapping parameters observed during preoperative assessment of PD patients evaluated for Deep Brain Stimulation. OFF = Measurement after at least 12 hours off usual dopaminergic medication, ON = Measurement at least 1 hour after administration of usual medication. P values relate to Mann Whitney U test. Datasets with too few taps (<20) were not eligible for analysis and do not have a corresponding ON/OFF state datapoint on the graph.


p=6.95x10^-2
Mean InterTapInterval
p=1.80x10^-2
STD InterTapInterval
p=2.31x10^-2
Error rate
p=0.42
Mean tap duration
p=0.26
STD tap duration
p=1.23x10^-2
SD1
p=1.59x10^-2
SD2
1e6
p=1.23x10^-2
Ellipse area
p=0.70
SDratio
p=0.14
Approximate entropy
p=1.38x10^-2
DFA
p=0.11
Sample entropy
OFF
ON
Stimulation



Changes in finger tapping parameters observed during post-operative assessment of PD patients with Subthalamic Nucleus Deep Brain Stimulation. OFF = Measurement with the stimulator switched off, ON = Measurement with the stimulator on. Patients were examined whilst on usual dopaminergic medication in both conditions. P values relate to Mann Whitney U test.


p=0.31
Mean InterTapInterval
p=3.50x10^-2
Error rate
p=0.12
STD InterTapInterval
p=0.47
Mean tap duration
p=1.00
STD tap duration
p=8.90x10^-2
SD1
p=8.90x10^-2
SD2
p=0.57
SDratio
p=0.10
Ellipse area
p=0.27
Sample entropy
p=0.52
DFA
p=0.34
Approximate entropy
p=0.38
Frequency diff. max to min
p=0.97
Frequency diff. Q1 to Q4
p=0.38
Frequency dominant
p=1.00
Frequency max
p=0.47
Frequency mean
p=0.52
Frequency stdev
OFF
ON
Stimulation



Changes in finger tapping parameters observed during postoperative assessment of PD patients with Globus Pallidus Interna Deep Brain Stimulation. OFF = Measurement with the stimulator switched off, ON = Measurement with the stimulator on. Patients were examined whilst on usual dopaminergic medication in both conditions. P values relate to Mann Whitney U test.

STN vs GPi target selection

The physiological differences between the two targets warrant further exploration. Initially, the GPi was a more favoured surgical target for DBS. This stemmed from the historical success of pallidotomy in the 1980s and 90s (Laitinen et al., 1992). With the GPi-DBS being highly effective, the consensus was that it should be a default option for symptomatic treatment of late PD (Williams et al., 2014). As more evidence from

primates emerged, the STN was suggested as an alternative choice, and the first STN-DBS systems were implanted (Aziz et al., 1992, 1991).

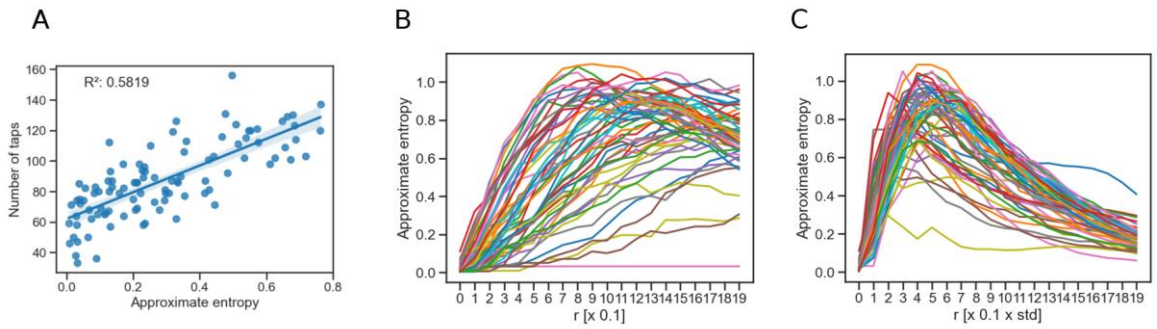
The selection of patients for an appropriate target remains an ongoing debate (Deep-Brain Stimulation for Parkinson's Disease Study Group et al., 2001; Okun and Foote, 2005; Wong et al., 2020). Candidates for DBS surgery are evaluated by a multi-disciplinary team (MDTs), including professionals specialising in neurology, neurosurgery, psychology, speech and language, and physical therapy – all assessing various aspects of PD symptoms and contributing to the decision about the optimal surgical intervention (Morishita et al., 2011; Okun and Foote, 2010). One study reported that over a third of DBS treatment failures could be mitigated by a more appropriate candidate selection (Okun et al., 2005). MDTs do an invaluable amount of work, often producing comprehensive reports, insightful discussions and suggestions based on hours of assessment and patient and family contacts. They provide the framework for selection, hospital care and post-operative follow-up for patients undergoing DBS surgery. However, many MDT members feel that the current tools of clinical assessment lack the precision and objectivity to allow them to examine specific symptoms, especially within the realm of gait and upper body bradykinesia. The purpose of this chapter was to conduct a pilot study on the feasibility and clinical utility of a device that could support the MDT members in making more informed decisions. In that, delineating features that are sensitive to changes in pre and postoperative status of patients was of key importance.

Approximate entropy

An unexpected finding of worsening ApEn warrants further exploration. ApEn is classically used on longer streams of data. In the initial paper, Pincus proposed at least 1000 datapoints (Pincus, 1991), however, some authors suggested smaller samples should suffice. Yentes and colleagues took this argument further, stipulating that even $N<200$ datapoints should yield good ApEn and SampEn values, provided parameters are selected carefully (Yentes et al., 2013). The main interpretative danger lies in the fact that a higher value of entropy may, in some scenarios, be a mere metric of more data points recorded. This would mean that the ITI duration series is indeed random but that a valid

calculation can only be performed with a certain threshold of data points supplied – illustrating a floor effect of the ApEn algorithm. This could create a paradox of improving ApEn after administration of medication or commencement of stimulation. The choice of function parameters could also influence the ApEn value in very small datasets (Yentes et al., 2013). These two potential sources of bias will now be discussed.

There was a clear correlation between the number of taps and ApEn values (R2 = 0.58, Fig 5.10A), suggesting that the above claim may hold at least partial validity. An attempt could be made to mitigate this bias by applying noise filtering through changes in the r parameter of the ApEn algorithm. The choice of r is highly debated, as explained in the methods section. Some advocate the use of r dependent on the standard deviation of the sample and plotting the ApEn values to find the maxima of the function (Delgado-Bonal and Marshak, 2019). When this analysis is applied to the levodopa challenge dataset, the following patterns emerge (Fig 5.10B and C). Plot C clearly resembles the reference graph from the Delgado-Bonal and Marshak paper, suggesting that the choice of 0.3 x standard deviation of the individual dataset analysed could be a reasonable adjustment. When corrected, the ApEn metrics showed a more expected trend. There was an improvement from a median of 0.79 (IQR 0.19) to a median of 0.69 (IQR 0.17) p=0.07 after the reintroduction of levodopa medication, showing a more expected reduction in randomness of the dataset. However, caution should be applied when interpreting this result, especially in the light of no difference being detected in the SampEn or DFA. Similarly, there was no difference in STN ON/OFF conditions: median 0.83 IQR 0.11 on, median 0.78 IQR 0.29 off stimulation, p=0.41. A safer conclusion would be to discount entropy analysis as a useful tool for benchmarking such a small (N<70) dataset. ApEn, SampEn and DFA are valuable algorithms but are perhaps better suited to larger and richer streams, e.g. long recordings of IMU, ECG or EMG data, as previously demonstrated in the literature.



Exploration of reasons for unexpected approximate entropy measures across all samples collected in this study (pre and post operative). (A) Correlation between the number of taps and approximate entropy showing a linear relationship between the measure of randomness and more data points being available. Plots of the approximate entropy values for different noise filters (r), first (B) as fixed digit (in 0.1 increments) and second (C) as multipliers of standard deviation of a time series (multipliers increased in 0.1 increments).

9

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Carthago delenda est.