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“INNOVATIVE METHODOLOGIES AND APPROACHES FOR ASSESSING BRADYKINESIA AND RELATED FEATURES IN PARKINSON’S DISEASE”

Supervisor:

Prof. Matteo Bologna

PhD student:

Antonio Cannavacciuolo

1397259

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Abbreviations

2D: Two-Dimensional: **3D:** Three-Dimensional: **AD:** Alzheimer's disease; **AI:** Artificial Intelligence; **ANOVA:** Analysis of Variance; **AUC:** Area Under the Curve; **BDI:** Beck's Depression Inventory; **BIC:** Bayesian Information Criterion; **CI:** Confidence Interval; **CKS:** Combined Kinematic Score; **CNNs:** Convolutional Neural Networks; **CoV:** Computer Vision; **CV:** Coefficient of Variation; **DAT SCAN:** Dopamine Transporter Scan ; **DAT:** Dopamine Transporter ; **ET:** Essential Tremor ; **ET-plus:** Essential Tremor Plus ; **FPS:** Frames Per Second; **GMM:** Gaussian Mixture Model; **HCs:** Healthy Controls; **ICC:** Intraclass Correlation Coefficient; **LEDD:** Levodopa Equivalent Daily Dose; **MDS-UPDRS:** Movement Disorder Society - Unified Parkinson's Disease Rating Scale; **ML:** Machine Learning; **MoCA:** Montreal Cognitive Assessment; **MPS:** Mild Parkinsonian Signs; **PD:** Parkinson's Disease; **pre-SMA:** pre-Supplementary Motor Area; **RBD:** REM Sleep Behaviour Disorder; **Rhythm^{C}:** Clinical assessment of movement rhythm (hesitations/halts); **Rhythm^{K}:** Kinematic rhythm (coefficient of variation of inter-tap intervals); **ROC:** Receiver Operating Characteristic; **SD:** Standard Deviation; **Seq Eff^{C}**: Clinical assessment of sequence effect; **Seq Eff^{K}**: Kinematic sequence effect; **SPECT:** Single Photon Emission Computed Tomography; **Vel^{C}:** Clinical assessment of movement velocity; **Vel^{K}:** Kinematic velocity

1. ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder marked by a heterogeneous constellation of motor and non-motor symptoms. Among its cardinal features, bradykinesia—defined as slowness of movement and a reduction in amplitude or speed (sequence effect) during continued movements—is essential for clinical diagnosis. However, increasing evidence suggests that bradykinesia is not specific to PD, as it can be observed in patients with other movement disorders, such as essential tremor (ET), in other neurological disorders not primarily characterized by parkinsonism, and even in healthy elderly individuals. The presence of overlapping motor features across various conditions complicate diagnostic accuracy and underscore the need for objective and fine-grained assessment tools to assess motor function.

The present thesis addresses the phenomenology and pathophysiology of bradykinesia in large cohorts of patients with PD, ET, and healthy older adults, employing high-resolution kinematic recordings and markerless computer vision (CoV) movement analyses in three different experimental studies. Our framework draws upon the recently proposed concept of the "bradykinesia complex," which decomposes bradykinesia into four fundamental components: movement slowness, hypokinesia, dysrhythmia, and the sequence effect.

Our findings demonstrate that specific combinations of kinematic features—particularly the presence of slowness, irregular rhythm, and sequence effect—are highly predictive of PD, while isolated motor slowness is a non-specific finding. Moreover, we validated the use of markerless CoV techniques as a reliable, scalable, and non-invasive alternative to traditional optoelectronic systems. These approaches yielded high concordance with clinical assessments and hold significant promise for remote patient monitoring.

By integrating objective motion analysis and artificial intelligence–based video assessment, this thesis contributes to the development of precision tools for differential diagnosis and disease monitoring in movement disorders and other conditions. Furthermore, it highlights the potential of telemedicine and environmentally sustainable models of care, paving the way for broader implementation in clinical neurology.

2. INTRODUCTION

2.1 Bradykinesia in Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder of the central nervous system. It was first described in 1817 by James Parkinson in his essay An Essay on the Shaking Palsy [1]. Today, PD is the second most common neurodegenerative disorder in developed countries, following Alzheimer's disease (AD) [2,3]. PD symptoms include both motor and non-motor manifestations. Key motor symptoms include bradykinesia, muscular rigidity, and resting tremor (4–6 Hz) [4]. Motor symptoms in individuals with PD are highly heterogeneous in terms of onset, distribution, severity, and response to therapy [5]. This variability has led to attempts to classify distinct subtypes of the disease. Two major subtypes have been proposed: (1) tremor-dominant PD and (2) non-tremor-dominant PD, which includes phenotypes such as akinetic-rigid syndrome and postural instability gait disorder. The disease course and prognosis differ between these subtypes; the tremor-dominant form is often associated with a slower progression and a lower degree of functional disability compared to the non-tremor-dominant form [6].

The diagnosis of PD is primarily clinical and based on the presence of parkinsonian motor features—specifically, bradykinesia plus rigidity and/or resting tremor [7]. These criteria rely on clinical features and are supplemented by special imaging techniques. Although no imaging technique can confirm the diagnosis of PD, visualization of the striatal dopamine system (mainly with the use of 123I-ioflupane single-photon-emission computed tomography [SPECT] or 18F-labeled fluorodopa positron-emission tomography) can differentiate between PD and disorders such as ET [8]. However, clinicopathological studies indicate that up to 25% of patients diagnosed with PD during life receive an alternative

diagnosis at postmortem examination. The rate of misdiagnosis is even higher in the early stages of the disease or when differentiating PD from atypical parkinsonian syndromes [9]. Beyond motor symptoms, PD should be considered a multisystem neurological disorder characterized by a wide range of non-motor symptoms, including olfactory dysfunction, cognitive impairment, psychiatric symptoms, sleep disturbances, autonomic dysfunction, pain, and fatigue [5,10,11]. These non-motor features are common in early PD and may precede the onset of classical motor symptoms by several years.

Although motor symptoms remain central to diagnosis, non-motor features are increasingly recognized for their diagnostic and prognostic value. Acknowledging the significance of these symptoms, in 2015, a task force of the International Parkinson and Movement Disorder Society (MDS) introduced new clinical diagnostic criteria for PD [7].

Motor symptoms such as bradykinesia and tremor typically present asymmetrically. Over time, the progression to bilateral bradykinesia, rigidity, tremor, and disturbances in gait and balance contributes to increasing functional impairment and loss of independence, often resulting from the combined impact of motor and cognitive deterioration, as well as falls and fractures.

The term “bradykinesia” literally refers to slowness of movement but is also used to describe low-amplitude movements (hypokinesia) and the absence of movement (akinesia), including both voluntary and spontaneous automatic movements [12]. According to the diagnostic criteria for PD, bradykinesia is defined as "slowness of movement and a reduction in amplitude or speed (sequence effect) during continued movements"[7,12,13]. The sequence effect is characterized by a progressive decline in speed and amplitude during repetitive actions and it is significantly more common in PD compared to atypical parkinsonisms.

While limb bradykinesia is essential for diagnosing PD it also affects other domains, including the voice (hypophonia), axial and gait movements, and facial expressions. Reduced facial expressivity, known as hypomimia, defined as reduced facial expressiveness, which can affect spontaneous facial movements like blinking or other facial movements, as well as the expression of emotions. In recent years, the concept of the bradykinesia complex has been introduced to highlight that bradykinesia is a multifaceted phenomenon encompassing several interrelated motor features—such slowness, reduced amplitude, irregular rhythm, and the sequence effect —reflecting the broader disruption of motor control networks in PD.

Bradykinesia and associated movement impairments are often evaluated through repetitive tasks, such as the classic finger-tapping test performed one hand at a time, which reveals declining speed and amplitude. The clinical evaluation of bradykinesia in PD and atypical parkinsonisms currently relies on specific clinical rating scales. Among these, Part III of the MDS Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is the most widely used tool for assessing motor function (Goetz et al. 2008; Antonini et al. 2013). In evaluating limb bradykinesia, the clinician rates speed, amplitude, hesitations, and halts or decrement during ten repeated movements, with each feature contributing equally to the final score. In the later stages of PD, additional deficits emerge, including delays in initiating voluntary movements or complete cessation of motor activity. Repetitive finger tapping is commonly used to assess bradykinesia in PD. This task represents a simple, accurate, and reproducible indicator of motor impairment. Previous kinematic studies have evaluated the worsening of motor performance in patients by investigating the changes in speed and amplitude with task completion, especially during finger tapping [14,15]. The hand opening/closing and hand pronation/supination tasks of the motor section of Part III of the Unified Parkinson's

disease rating scale were instead less accurate in detecting these abnormalities. Moreover, motor impairment presents specific features in PD depending on different stages of the disease. Bologna et al., have demonstrated, that bradykinesia, hypokinesia, and altered movement rhythm are more prominent in the advanced stages of the disease whereas the sequence effect is present in early PD but not in advanced PD [16]. Finally, the characteristics of repetitive finger movements have been assessed also in atypical parkinsonism (e.g., PSP). It has been reported that atypical parkinsonisms are mostly characterized by hypokinesia without progressive decrement, whereas the characteristic pattern of decrease in the amplitude and velocity of finger tapping (sequence effect) does not occur[17]. These evidences suggest that the evaluation of these movements could be helpful for differential diagnosis between PD and atypical parkinsonisms [18,19].

2.2 Bradykinesia in non-parkinsonian conditions

Numerous clinical and experimental studies have demonstrated that bradykinesia can be observed in various neurological disorders that are not primarily characterized by parkinsonism. These include hyperkinetic movement disorders such as dystonia or chorea [20,21], and, notably, ET [22–28]. Furthermore, bradykinesia has been observed in neurodegenerative diseases that are not classified as movement disorders. These include conditions involving the cerebellum and corticospinal system [14,29], as well as multiple sclerosis [30–32], psychiatric disorders [33] and dementia [34–39]. In contrast to PD, the clinical and neurophysiological characteristics of bradykinesia in non-parkinsonian conditions are not well-defined, and it remains unclear whether the same network responsible for bradykinesia in PD is also implicated in these conditions.

Focusing on ET, the presence of bradykinesia is not a routinely manifestation. It is well-documented that some patients with ET may develop parkinsonian signs over time and are more likely to have a family history of PD [40,41]. Although not officially recognized in classifications, the term ET-PD has been frequently used in the literature to describe ET patients presenting with parkinsonian syndrome symptoms that do not meet the criteria for idiopathic PD [41–45]. When bradykinesia, considered a "soft neurological sign," is observed, the revised tremor classification recommends the use of the term "ET-plus" [46]. Numerous clinical reports have described slowness of movement in ET, but findings remain inconsistent and debated [47–50]. On contrary, only a limited number of studies have objectively assessed movement slowness during voluntary movements in patients with ET, in particular during the execution of prono-supination movements, or of oscillatory movements, or in association with hypokinesia [23,25,51]. In clinical practice, however, the most used motor task to evaluate bradykinesia is represented by repetitive finger movements, and to date, few kinematic studies have used this task. Recent studies have revealed that ET patients present a slowing of movement without the sequence effect typically seen in PD, and this phenomenon does not correlate with the severity of postural and kinetic tremor (Bologna et al., 2020). Additionally, ET patients display intermediate velocity levels between those observed in PD patients and healthy controls (HCs), with kinematic patterns shared by both groups in cluster analyses. These findings suggest that bradykinesia in ET should be understood as purely motor slowness without decrement, and that may reflect a distinct pathophysiological mechanism, differing from the sequence effect of PD and the action tremor characteristic of ET (Bologna et al., 2020).

Moreover, the presence of bradykinesia is also clearly observed in healthy elderly individuals as documented in several studies [52–55]. Bennet et al. found that signs of

parkinsonism are common in older people and are associated with an increased risk of death, particularly when a gait disturbance is present. In 2016, a report by Buchman and colleagues evaluated the frequency of parkinsonism in the elderly and its association with adverse health outcomes and postmortem indicators of brain disease. Results showed that about 26% of participants had parkinsonism, with a higher prevalence in older age groups. Parkinsonism was also associated with an increased risk of death, mild cognitive impairment, Alzheimer's disease, and disability. In a 2021 paper, Buchanan and colleagues conducted a systematic review on Mild Parkinsonian Signs (MPS), examining their clinical, imaging and pathological associations. MPSs have been extensively studied over the past three decades and proposed as risk markers for neurodegenerative diseases. The review found that MPS are common in the elderly and may be associated with structural changes in the brain, suggesting that they may represent a prodromal stage of more severe movement disorders. In 2025, using kinematic analysis, De Riggi and colleagues investigate how aging and frailty affect motor performance. Results showed that aging and frailty lead to reduced motor efficiency, with frail individuals displaying greater variability in movement patterns, emphasizing the value of kinematic analysis in detecting early motor decline and underscoring frailty as a critical factor in age-related motor impairment.

2.3 Pathophysiology of Bradykinesia

The specific mechanisms behind bradykinesia in PD remain partially understood. Although traditionally associated primarily with dopaminergic denervation in the basal ganglia and dysfunction of striato-cortical circuits [56–58], emerging research suggests that other brain regions may also contribute to the pathophysiology of bradykinesia [59–65]. Recent studies propose that bradykinesia in PD results from a broader network dysfunction, primarily

involving the basal ganglia, sensorimotor cortical areas, and the cerebellum. [13]. Central to its pathophysiology is the disruption of basal ganglia-thalamo-cortical circuits, particularly the imbalance between the direct and indirect pathways, which leads to excessive inhibitory output from the internal segment of the globus pallidus (GPi) and the substantia nigra pars reticulata (SNr) toward the thalamus. This heightened inhibitory drive diminishes thalamo-cortical facilitation, ultimately impairing the initiation and scaling of voluntary movements [57,66,67]. Moreover, electrophysiological studies have demonstrated that the primary motor cortex (M1) in PD patients exhibits aberrant beta-band synchronization with basal ganglia structures, a phenomenon that correlates with motor slowness and rigidity [59,61,68]. The supplementary motor area (SMA), which is crucial for motor planning and the temporal organization of sequential movements, also shows reduced functional connectivity and impaired activation patterns, particularly in tasks requiring internal generation of movement [61,69]. In parallel, cerebellar contributions—typically involved in error correction and sensorimotor integration—appear functionally disconnected from the cortical motor areas and the basal ganglia in PD, which may exacerbate deficits such as the sequence effect [64,70]. Additionally, altered activity in parietal and somatosensory cortices suggests a deficit in proprioceptive integration and feedforward control mechanisms, further contributing to the impaired modulation of movement amplitude and velocity observed in bradykinesia [71,72].

Supporting the view of bradykinesia as a network disorder, recent evidence demonstrated that the different features of bradykinesia variably respond to dopaminergic medications. In this regard, it is known that Levodopa administration improves the movement speed and amplitude but not the sequence effect. This suggests that the pathophysiological mechanisms of the sequence effect probably involve non-dopaminergic neurotransmitter

systems [73,74]. Neural networks outside basal ganglia circuits may also have a role in this phenomenon. Dysfunction of cortical motor areas controlling voluntary movements, including primary and non-primary motor areas or their connections, can be involved [73,74]. Neurophysiological studies investigating the neural correlates underlying micrographia, a handwriting disorder characterized by progressively abnormally small or consistently reduced writing [75], in PD have demonstrated that the sequence effect may be independent of dopaminergic pathways. Probably, the dysfunction of some areas involved in controlling sequential movements, e.g., the rostral supplementary motor area (pre-SMA) or cerebellum, may be associated with progressive micrographia [76]. Therefore, this abnormality is probably connected to a combination of dysfunctions of circuits involved basal ganglia, the pre-supplementary motor area, rostral cingulate motor area, and the cerebellum[59,76].

As seen in previous neurophysiological studies, bradykinesia could potentially be due to anomalies in movement programming and execution [56]. The altered scaling of the dynamic muscle force to the movement parameters has been suggested to contribute to bradykinesia [77]. Also, abnormalities of sensorimotor integration can play an important role in the physiopathology of bradykinesia, as described in the various types of movement disorders. Disturbances of proprioceptive processing, related to abnormal muscle-stretch reflexes, might also be relevant for generating hypometric or bradykinetic movements [15,78,79].

Moreover, PD and some atypical parkinsonisms are characterized by facial motor impairment, which is represented by alterations in both spontaneous and voluntary movements, to which is added an alteration of facial expressions, also called hypomimia. In

particular, this latter consists of a reduction of spontaneous blinking and an impairment of emotional facial expressions [5,80,81]. Hypomimia is usually bilateral and symmetrical although, in up to about 5% of patients with PD, one-half of the face may be more affected than the contralateral half (hemihypomimia), ipsilateral to the most affected side of the body and where symptoms began [82]. In addition to these features, an altered ability to mimic a facial expression shown in an image (posed emotions) and an impaired emotion recognition were also widely reported in different studies, which showed that probably these two deficits share the same underlying pathophysiological mechanisms [82–86]. In PD patients, neurophysiological studies show that voluntary orofacial movements are reduced in amplitude and slower in velocity, while voluntary blinking presents normal speed and amplitude, although there is an increase in the interphase pause between opening and closing the eyes and was only partially reduced by dopaminergic treatment [87]. In PD, dysfunction of the basal ganglia would appear to represent the underlying substrate of facial motor control abnormalities. The sparing of some elements of upper facial movement (i.e., voluntary blink kinematics) in PD could be secondary to distinctive physiological features of the facial motor control system, such as the presence of ipsilateral and contralateral innervation of the upper portion of the face by frontal cortical areas or lower eyelid inertia during blinking could be a safety factor for the development of bradykinesia [80,87]. Indeed, while the impaired expression of emotions in PD is likely to reflect impaired basal ganglia loops and abnormal primary motor and pre-motor area activation in the frontal lobe, the specific impairment of emotion recognition in PD is likely to reflect a predominant involvement of limbic system components, including the insula and amygdala [83].

2.4 Kinematic and computer vision analysis

The clinical evaluation of bradykinesia in PD and atypical parkinsonisms is subject to intra- and inter-individual variability and limited reliability across the various UPDRS items, which may impact therapeutic outcomes and consistency in research settings [12,13] .

To enhance the reliability of bradykinesia assessment, several technology-based tools have been introduced [88,31]. For instance, kinematic optoelectronic systems track reflective markers placed on specific body points as patients perform various motor tasks. By applying kinematic protocols to repetitive finger tapping, researchers can quantify specific aspects of voluntary movement—such as movement count, speed, amplitude, rhythm, and the decrement in amplitude and speed known as the sequence effect [89]. These analyses yield continuous data regarding the type and severity of bradykinesia and the patient's therapeutic response in both PD and atypical parkinsonisms [16,17].

In early PD, mild bradykinesia and hypokinesia with sequence effect are commonly observed, while in advanced stages, these features become more pronounced [16]. In contrast, hypokinesia without decrement is a distinguishing feature of progressive supranuclear palsy compared to PD and multiple system atrophy [17,18]. Additionally, abnormalities in voluntary movement have been documented in non-parkinsonian conditions, even when not clinically apparent. Movement slowness has been observed in hyperkinetic disorders (e.g., ET, dystonia), iatrogenic and cerebellar disorders, motor neuron diseases, and cognitive disorders, where bradykinesia may or may not be accompanied by other motor abnormalities [13,26,89–91] .

Kinematic analysis offers a valuable means of characterizing bradykinesia both in terms of phenomenology and etiology, aligning with recent definitions [12]. Nonetheless, overlapping phenomenology among patient groups often prevents etiological diagnosis

based solely on bradykinesia features. Paparella et al. demonstrated that kinematic techniques can distinguish PD patients with moderate-to-severe bradykinesia from individuals with normal movement velocities. However, about 30% of individuals (including PD, ET, and healthy subjects) with mild-to-moderate abnormalities remained difficult to classify. Thus, kinematic findings should always be interpreted in conjunction with broader clinical data to establish an accurate diagnosis [92].

Optoelectronic systems can also objectively assess tremor characteristics—such as amplitude, frequency, distribution, activation conditions, temporal changes, and medication responsiveness [93]. These systems may assist in more precisely characterizing additional features of ET-plus, particularly when supported by laboratory data [46]. Recently, Angelini et al. identified soft signs like rest tremor and bradykinesia in ET-plus patients through clinical and kinematic analysis. The presence of more severe and widespread action tremor in those with rest tremor, along with mismatched lateralization of rest tremor and bradykinesia, may point to distinct pathophysiological mechanisms underlying these soft signs [94].

Despite their potential, kinematic techniques are not yet standardized. Different laboratories employ various protocols and assessment criteria, often relying on internal reference databases for both clinical and research purposes. To establish these methods as standardized diagnostic tools, future clinical studies involving larger patient cohorts will be essential to further validate and refine the characterization of motor abnormalities [92,93].

Video recording has long been a fundamental tool in the clinical practice of movement disorders. It provides an objective documentation of the neurological examination, captures subtle qualitative and quantitative aspects of movement over time, and enhances the

medical record, while also serving as an invaluable educational resource [95]. In cases of diagnostic uncertainty or interpretative disagreement, video footage allows clinicians to re-examine motor phenomenology even in the absence of the patient [95,96].

In recent years, the integration of video recording with advanced artificial intelligence (AI) and machine learning (ML) technologies has opened new avenues for the objective analysis of motor disorders, also leveraging the widespread availability of high-definition, user-friendly smartphone cameras [97,98]. In particular, the application of computer vision (CoV)—a subfield of both AI and ML—has enabled the automatic processing of visual data (images and videos) through pose estimation algorithms that detect the position of anatomical landmarks without requiring physical markers. This markerless methodology allows for three-dimensional tracking of body movements and the reconstruction of skeletal models directly from video, even in uncontrolled environments [99]. Pose estimation is the cornerstone of the CoV operational sequence, as it relies on the identification and tracking of anatomical landmarks that are essential for subsequent kinematic analysis. Widely used systems such as OpenPose, MediaPipe, and DeepLabCut enable the extraction of kinematic variables such as position, velocity, and trajectory. Specifically, OpenPose and MediaPipe are suitable for multi-person tracking in dynamic settings and have been used in the analysis of gait, finger tapping, and tremor, while custom 3D models focus on the fine-grained tracking of hands and fingers [97,100]. DeepLabCut, on the other hand, enables frame-by-frame tracking and has proven useful in the study of both bradykinesia and dystonia [97,100,101]. Once the skeletal data are generated, quantitative variables are extracted to describe joint relationships during motor task execution; these variables then feed into predictive ML models, which can be used to classify movements (e.g., normal vs. pathological) or to estimate clinical scores.

This technology has demonstrated particular effectiveness in the objective evaluation of bradykinesia, tremor, and dyskinesias. Automated analysis of finger tapping videos has shown sensitivity and specificity exceeding 90% in distinguishing patients with PD from healthy controls, with strong correlations to MDS-UPDRS scores [102]. Deep learning algorithms have also been successfully applied to detect and quantify levodopa-induced dyskinesias, achieving high diagnostic accuracy (AUC up to 0.93) and strong correlations with established clinical rating scales [103]. Promising results have also been obtained in gait analysis—through posture recognition systems integrated with eye fixation data—and in the evaluation of facial hypomimia, where CoV has enabled the automatic detection of reduced emotional expressivity in PD patients [104–106]. Beyond PD, CoV applications are rapidly expanding to encompass other movement disorders, including ET, chorea, dystonia, ataxia, and tic disorders [107–111].

Although ordinal rating scales for clinical assessment of bradykinesia are widely used, they represent a significant oversimplification of a highly heterogeneous motor phenomenon. The ability to quantify subtle parameters such as movement speed, amplitude, and rhythm allows for a more detailed and reproducible analysis, yielding clinically relevant insights that often escape traditional observation. In this context, markerless CoV techniques emerge as highly promising tools for continuous, objective, and non-invasive monitoring of motor symptoms, with potential applications both in clinical settings and in home-based telemedicine scenarios.

Although they were not directly investigated in the experimental studies presented in this thesis, in recent years, in addition to well-established motion analysis techniques, such as optoelectronic systems and, more recently, markerless video-based algorithms, there has been growing interest in the use of wearable devices among the available technologies for

the quantitative assessment of bradykinesia and movement disorders in Parkinson's disease [112,113]. These tools, based on miniaturized inertial sensors (including accelerometers, gyroscopes, and magnetometers), are applied directly to the patient's body, typically on the upper or lower limbs, and enable continuous recording of movement in real-world, unsupervised environments [114–116]. The adoption of wearable technology has steadily expanded in both clinical and research settings due to its ability to provide reliable quantitative measurements of bradykinesia, tremor, freezing of gait, and other parkinsonian motor symptoms [114,117,118]. These devices have demonstrated utility not only in assessing motor impairment during the diagnostic phase but also in the long-term monitoring of motor fluctuations and in evaluating treatment efficacy [119]. They are particularly effective in detecting motor patterns that may escape episodic clinical observation, such as intra-individual variability or the emergence of transient symptoms [119]. The integration of wearable systems into clinical practice offers a significant step toward personalized medicine, as the systematic and continuous acquisition of motor data—combined with artificial intelligence algorithms—may facilitate the early identification of specific phenotypes and the stratification of patients into clinically meaningful subgroups, ultimately contributing to the optimization of individualized treatment strategies [120]. Nevertheless, several challenges still hinder their widespread implementation in routine care, including the lack of standardization among commercially available devices, the need for large-scale clinical validation, and the importance of developing user-friendly interfaces for both patients and clinicians. Despite these limitations, wearable devices are playing an increasingly important role, particularly in community-based medicine and telemedicine, as complementary tools to conventional neurological assessments [121].

The integrated application of clinical assessment and kinematic motion analysis represents a valuable approach for detecting bradykinetic motor impairment not only in PD, but also in other neurological or age-related conditions. Moreover, it enables an objective quantification of the specific components of bradykinesia—namely, alterations in movement rhythm, velocity, and amplitude—and facilitates the identification of distinct patterns of these features across both pathological and physiologically aging populations.

In light of recent developments in the application of CoV and deep learning, it is interesting to evaluate the use of markerless techniques in the automatic assessment of bradykinesia, comparing their performance with that of traditional kinematic systems. Within this framework, the project "Telemedicine methods in the assessment of parkinsonian patients to reduce travel to outpatient clinics and protect the environment", co-funded by the *Programma Operativo Nazionale Ricerca e Innovazione - Azione IV.5 "Dottorati su tematiche Green"*, aims to evaluate the correlation between the clinical severity of bradykinesia, as assessed through standard neurological examination, and data obtained from the automated analysis of video recordings acquired via smartphone and from laboratory-based motion analysis systems.

The ultimate objective is to validate markerless technologies as reliable, scalable, and non-invasive tools for the objective quantification of motor symptoms, suitable for both clinical settings and remote telemedicine applications. Widespread adoption of such methods could not only improve access to diagnosis and monitoring for PD patients but also significantly reduce the need for travel, contributing to the environmental sustainability of healthcare systems.

3. EXPERIMENTAL PART

3.1 STUDY 1: May bradykinesia Features Aid in Distinguishing Parkinson's Disease, Essential Tremor, And Healthy Elderly Individuals?

3.1.1 Introduction

Bradykinesia (movement slowness) and associated motor features (hypokinesia, i.e., reduced movement amplitude, hesitations/halts and sequence effect) characterize the motor phenotype of PD and atypical parkinsonism [7,12,13,122–126]. Nevertheless, bradykinesia can be also observed in various neurological conditions [90] and in elderly healthy subjects [52–54]. Although the clinical examination has been deemed the gold standard for evaluating bradykinesia, it is hindered by limited reliability, coupled with inter and intra-rater variability [13,88,90,127–130]. Interpreting objective bradykinesia data, obtained through kinematic techniques is an especially challenging task, particularly when utilized for diagnostic purposes [13,131,132]. In a recent study, we utilized a kinematic motion system to objectively evaluate finger tapping movements in patients suffering from PD and ET, as well as healthy controls (HC) [26]. Despite showing distinct motor traits between PD, ET, and HC at the group level, the examination of individual data revealed a significant overlap in kinematic measures across the three cohorts. Consequently, we faced difficulty in precisely predicting the accurate diagnosis upon considering individual bradykinesia features. In light with the marked overlap characterizing the features of bradykinesia and also considering that a broad spectrum of neurological conditions may underlie this motor disorder, we recently proposed a dual-axes approach to bradykinesia [12]. Axis I concerns the phenomenology of bradykinesia and its associated features, while axis II concerns the possible bradykinesia etiology [12]. Accordingly, we posited that certain combinations of bradykinesia features could offer hints about specific etiologies. For instance, bradykinesia

combined with sequence effect and other features strongly points to parkinsonism. Conversely, isolated bradykinesia (movement slowness alone) is a non-specific finding that may manifest in various neurological conditions [12]. Further studies, however, are needed to better address the relationship between bradykinesia phenomenology (Axis I) and its etiology (Axis II). In this study, we analyzed the kinematics of three groups commonly encountered in the movement disorder outpatient clinic: patients with PD, ET, and elderly individuals who may exhibit subtle parkinsonian signs. Also, we investigated whether clinical and kinematic evaluations of bradykinesia could aid in classifying individuals without *a priori* diagnosis. The study's results were interpreted in the context of our recently published viewpoint on bradykinesia [12].

3.1.2 Materials and Methods

Participants

One hundred and ninety subjects were enrolled in the study, including 44 PD patients (17 F, mean age ± standard deviation - SD: 67.84 ± 8.69 years), 69 ET patients (31 F, mean age ± SD: 68.42 ± 11.16 years), and 77 HC (44 F, mean age ± SD: 66.1 ± 8.14 years) (Table 1). Participants were consecutively recruited at the outpatient clinic of the Department of Human Neurosciences, Sapienza University of Rome. The diagnosis of PD and ET was based on clinical criteria [7,46,133]. PD patient with various phenotypes of the disease were enrolled, including patients with an akinetic-rigid form, as well as with tremor dominant phenotype [134,135]. Pharmacological therapies possibly acting on the central nervous system were discontinued in patients. In detail in PD, dopaminergic therapy discontinuation was performed at least 24 hours before the experimental evaluation [16,59,68,136]. In ET patients, therapy discontinuation was obtained by dose reduction in the week prior to evaluation,

with drug withdrawal 24 hours earlier for propranolol and benzodiazepines and 48 hours earlier for primidone and topiramate [26,91,93,137]. Demographic data and clinical information were collected (Table 1). Cognitive performance was tested in participants by using the Montreal Cognitive Assessment (MoCA) [138]. The study protocol underwent review and gained approval from the local Institutional Review Board, and all participants provided their written informed consent to undergo the experimental procedures.

Video recordings and evaluation

Participants were video recorded while repeatedly performing 15 s of opening and closing the index finger and the thumb (finger tapping) as fast as possible and with the widest range of motion [16,26,28,59,68,136]. Subjects performed finger tapping by holding their arm at roughly shoulder height, with the forearm semi-flexed and the wrist in line with the forearm [16,26,28,59,68]. PD patients performed the finger tapping with the most affected hand [16,26,59]. In light of previous investigations indicating no significant impact of handedness on motor performance, finger tapping assessments were performed with the dominant hand by both ET and HC [16,26,59]. The camera only captured the hand performing finger taps, disregarding facial and other body movements, assuring that the presence of other neurological indications, such as hypomimia or change in body posture, would not influence the assessment [95,129,130]. Finger tapping videos were randomized for participants' diagnosis, and a blinded clinical evaluation was performed offline based on video recordings. In detail, seven neurologists with expertise in movement disorders independently scored the tapping performance from 0 to 4, according to item 3.4 (finger tapping) of the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [139,140]. As per the MDSUPDRS protocol, raters were

requested to clinically assess movement velocity (VelC), hesitations/ halts (RhythmC), and decrementing amplitude (sequence effect or Seq EffC) while executing the tapping test. A rating of 0 denotes a normal motor performance, whereas a score of 1 indicates slightly impaired movements. Similarly, score 2 represents mild abnormal movements, while score 3 depicts a moderate tapping abnormality. Lastly, score 4 is indicative of a severe movement abnormality [139,140]. Besides the overall score, we asked evaluators to distinguish, using a binary system (yes or no), if the MDSUPDRS score assigned to a specific video was due to a) decreased movement speed, and/or b) modified rhythm, and/or c) sequence effect [129].

Kinematic recordings and analysis

We recorded the kinematics of repetitive finger tapping using a 3-D optoelectronic system (SMART motion system, BTS,Milan,Italy), consisting of three infrared cameras that detected the movement in three dimensional space of reflective markers placed on the body segments to be analyzed. Specifically, three markers were placed on the hand and two additional markers were placed on the distal phalanx of the index finger and thumb of the dominant hand in the ET and HC groups and on the most affected hand in the PD group. The cameras had a sampling rate of 120 Hz [16,28,39,59,89,93,141,142]. Motion analysis was conducted offline using specialized software (SMART Analyzer, BTS Engineering, Italy). Using an automatic algorithm, this software accurately identified several kinematic parameters, as described elsewhere [16,28,59,141]. In line with the clinical evaluation approach, we narrowed our focus for further analysis on kinematic data to movement velocity (VelK), expressed in degrees/s, movement rhythm (RhythmK), which is determined by the coefficient of variation computed by the ratio of standard deviation to mean value of inter-tap intervals. Higher values indicate a less regular repetition of movements. We also

considered the amplitude decrement (Seq EffK), expressed in degrees per number of movement[16,28,59,141]. It should be noted that the researcher responsible for the kinematic recordings and analyses (LA) was also blinded to the participants' diagnoses.

Statistical analysis

We analyzed gender distribution and familial history differences among PD, ET, and HC participants using the Chi-square test. Additionally, the Kruskal Wallis test was performed to investigate potential variations in demographic and clinical characteristics between the three groups, and post-hoc comparisons were conducted using Dunn's test. Fleiss' K was employed to calculate the interraters' consensus in the blinded video evaluation, whereby a value above 0.21 indicated a satisfactory level of agreement between raters in accordance with Landis and Koch's (1977) criteria [143]. KruskalWallis testing was utilized to compare clinical scores obtained from the blinded video evaluation of the three participant groups (mean of the 7 raters scores), and post-hoc comparisons were carried out with Dunn's test. The frequencies of observance for each motor abnormality—VelC, RhythmC, and Seq EffC—were compared between the groups through the Chi-square test. In addition, finger tapping kinematics were compared between PD, ET, and HC using one-way ANOVA, with kinematic variables analyzed in separate ANOVAs. Post-hoc analyses were performed using the Bonferroni test.

The possible correlations between clinical data, video scores, and kinematic parameters were assessed using Spearman's rank correlation coefficient. To evaluate the overlapping distribution of the kinematic data, clinical evaluation scores were analyzed and presented through stratified density plots. Furthermore, ordinal and multinomial logistic regression analyses were conducted to determine the impact of each kinematic variable on the

probability of belonging to a clinical score category (0, 1, 2, or 3-4) and a diagnostic group (PD, ET, or HC). To obtain a comprehensive assessment, a combined kinematic score (CKS) was developed by considering all the kinematic variables. The CKS was calculated by taking the linear combination of the coefficients derived from the ordinal logistic model. The resulting score accurately reflected the participant's overall kinematic performance.

$$CKS = -3.1\ Vel^{K}/1000 + 19.3\ Rhythm^{K} - 0.9\ Seq\_Eff^{K}$$

To ensure consistency, we normalized the CKS values to a range of 0 to 1 before proceeding, with a higher score reflecting more severe alterations. ROC curves were utilized for visualization and determination of the predictive power of each kinematic variable and the CKS for a particular diagnostic category. The area under the ROC curve (AUC) was used as a measure of discriminating capability for the model. We chose the optimal cut-off point based on the Youden index.

We set the level of significance at 0.05 and performed data analysis using R (version 4.2.2) and STATISTICA® (TIBCO Software Inc., Palo Alto, California, US).

3.1.3 Results

Demographic and clinical results

The analysis revealed no clear differences in gender ratio and age between PD,ET, and HC, and MoCA scores were statistically comparable among the three groups of participants ($p > 0.05$). As expected, the age of disease onset was significantly higher in PD than in ET ($p = 0.009$), while disease duration showed an opposite trend, being longer in ET than in PD ($p < 0.001$). Furthermore, while 50.73% of ET cases had a positive family history of tremor, no PD

patients reported a similar family history of parkinsonism or other neurological conditions (Table 1).

Video evaluation

Through our blinded finger tapping video evaluation, a fair global agreement was reached amongst raters (Fleiss $K = 0.34$). In particular, the Fleiss K was 0.3 for the PD group, 0.31 for ET, and 0.27 for HC. Kruskal-Wallis ANOVA indicated that there was a significant variance in the finger tapping scores between the three groups of participants[$H(2)=74.28$, $p < 0.001$]. Post-hoc comparisons showed higher scores in PD as opposed to ET and HC ($p = 0.012$ and < 0.001, respectively), as well as in ET as opposed to HC ($p < 0.001$) (Fig. 1A). Intriguingly, raters assigned an MDS-UPDRS finger tapping score of ≥ 1 to 149 out of 190 subjects, and details on finger tapping scores for each group can be found in Fig. 1B.

When considering the specific motor abnormalities responsible for the MDS-UPDRS finger tapping score (Fig. 1C), we observed that in PD patients, 43.8% had reduced Vel^C, 44.8% had altered $Rhythm^C$, and 67.2% had Seq Eff^C. In ET patients, 60.9% had reduced Vel^C, 44.9% had altered $Rhythm^C$, and only 36.6% showed Seq Eff^C (Fig. 1). In HC, we observed equal prevalence of the three motor abnormalities (reduced Vel^C - 24.48%, altered $Rhythm^C$- 30.98%, and Seq Eff^C- 28.75%), with no significant difference between any of them. In summary, movement slowness, which was identified in both PD and ET patients by the raters, proved to be the most prominent abnormality in movement. It was also observed that this abnormality differed between PD and ET, in addition to being much lower in the control group (all ps < 0.01, see Fig. 1 Legend for more details). On the other hand, although an irregular movement rhythm could differentiate controls from patients, it was not able to distinguish between PD and ET ($p = 0.55$). The sequence effect was found to be more

prevalent in individuals with PD than in those with ET and HC (both ps < 0.001). However, there was no significant difference observed between the occurrence of the sequence effect in ET and HC ($p = 0.15$).

Kinematic analysis of finger tapping

The kinematic parameters of finger tapping in the three groups are shown in Table 2. As expected, the ANOVAs disclosed a significant effect of the factor 'GROUP' for VelK ($F2,187 = 26.61$, $p < 0.001$), $Rhythm^K$ ($F2,187 = 10.04$, $p < 0.001$), and $Seq\ Eff^K$ ($F2,187 = 6.91$, $p = 0.001$). VelK was lower in PD as compared to both ET and HC ($p = 0.005$ and $p < 0.001$, respectively), as well as in ET as compared to HC ($p < 0.001$). $Rhythm^K$ was more irregular in PD than in ET and HC ($p = 0.005$ and $p < 0.001$, respectively), with no difference between ET and HC ($p = 0.48$). Finally, the $Seq\ Eff^K$ was higher in PD than in ET and HC ($p < 0.001$ and $p = 0.03$, respectively), with no difference between ET and HC ($p = 0.43$).

In summary, kinematic analysis of finger tapping revealed that subjects with PD exhibit bradykinesia, often accompanied by sequence effect an irregular rhythm, whereas the primary motor abnormality observed in subjects with ET and HC was an isolated bradykinesia.

Correlation analysis

We found a correlation between age and the median clinical score at the blinded video rating in participants ($R = 0.23$, $p = 0.001$). The analysis also showed an inverse correlation between video rating global scores and VelK values (r=-0.51, $p < 0.001$). Conversely, a direct relation was observed between video rating global scores and $Rhythm^K$ values ($r = 0.51$, $p < 0.001$). This means that the patients who obtained the highest scores at the blinded video

evaluation also showed the slower and the more irregular movement at the kinematic analysis. Notably, we did not find any correlation between clinical scores and the Seq Eff^K (r=-0.06, p = 0.38). Also, no correlations were found between kinematic values and tremor severity in ET (r = 0.12, p = 0.34), nor between other demographic, clinical, and kinematic data.

Stratified density plots

In Fig. 2, the distribution of kinematic parameter values in the participants is presented, based on the median score (ranging from 0 to 4) given by the 7 raters. Supplementary Figures 1, 2, and 3 depict the distribution of kinematic parameter based on the clinical score given by each rater. The density plots reveal a substantial overlap among the kinematic data curves, which suggests that a specific clinical score is associated with a broad range of kinematic values. Figure 2 also illustrates the distribution of kinematic parameters among the three groups of participants (PD, ET, and HC), displaying the lowest VelK values in the PD group (left-hand graph), with substantial overlap observed in both ET and HC groups. Notably, the kinematic data of Rhythm^K and Seq Eff^K demonstrated even greater overlap across all three groups (middle and right-hand graphs).

Ordinal and multinomial logistic regression analyses, ROC curves

The results of the ordinal and multinomial logistic regression analyses are presented in Fig. 3, which depicts the probability of being assigned to a specific clinical score category (0, 1, 2, or 3-4, Fig. 3A) or diagnostic group (PD, ET, and HC, Fig. 3B) based on individual kinematic parameters and CKS values. Notably, individuals with high CKS scores (>0.6) were more likely to be classified as clinically bradykinetic, with MDS-UPDRS clinical scores exceeding 2

(Fig. 3A). Conversely, those with low CKS scores (<0.2) had a high probability of being clinically classified as normal, with MDS-UPDRS clinical scores of 0. Intermediate CKS values were associated with a low probability of proper bradykinetic classification (Fig. 3A). Similarly, subjects with CKS values greater than 0.7 had a high probability of being in the PD group and a very low probability of being in the HC group (Fig. 3B). Conversely, individuals with low CKS scores (less than 0.2) had a high probability of being normal and a very low probability of being in the PD group (Fig. 3B). Again, intermediate CKS values were associated with equal probabilities of belonging to the PD, ET, and HC groups, reflecting more limited possibilities for proper diagnostic classification. ROC curves (Fig. 4) demonstrated that CKS cutoffs of 0.7 and 0.2 were highly specific for differentiating PD from HC [sensitivity: 0.136 (0.052, 0.274), specificity: 0.986 (0.951, 0.998), and sensitivity: 0.247 (0.156, 0.358), specificity: 0.938 (0.877, 0.975), respectively]. It is worth noting that the area under the curve (AUC) of the Vel^K parameter was comparable to that of the CKS, highlighting the crucial role of this kinematic parameter in assessing bradykinesia.

3.1.4 Discussion

Our study aimed to determine whether a comprehensive clinical and kinematic assessment of repetitive finger tapping could facilitate the detection of bradykinesia and accurately predict diagnoses across a range of PD, ET, and healthy elderly individuals. Our findings support previous evidence indicating that bradykinesia is a prominent feature of PD, but is also present in ET and, to a lesser extent, in otherwise HC [26,90]. We also noted that the features of bradykinesia differ depending on the group of subjects it occurs in. Specifically, bradykinesia with sequence effect and altered movement rhythm is more common in PD whereas bradykinesia alone is frequently observed in ET and HC. Alongside clinical

examination, kinematic analysis is crucial for accurate bradykinesia detection and patient categorization in most cases. However, our study also uncovered a complex relationship between bradykinesia phenomenology and the underlying etiology, and in approximately 30% of cases the diagnosis was not achievable. Demographic characteristics, such as age and sex distribution, of the PD, ET, and HC groups were similar, dampening the impact of these factors on our results. Cognitive performance was also comparable among the three groups, thus avoiding a potential confounding factor. Even though the diagnosis of PD and ET was determined by clinical criteria and without the use of DaTscan examination, all patients were consistently monitored in our outpatient clinic for several years, significantly mitigating the possibility of misdiagnosis bias [7,46]. To ensure the accuracy of our assessments, we took additional measures. First, all patients discontinued therapies 48 hours before the experimental evaluation to avoid any potential impact on finger tapping performance. Second, bradykinesia assessments were blinded to participants' diagnosis. Third, a blinded assessment of both videos and kinematic recordings was conducted to ensure that the evaluation of finger movement remained unbiased. Again, to avoid any external influence on the assessments, the video frames focused only on the subject's hand [129,130], thus eliminating the possibility that additional neurological symptoms, such as hypomimia or altered body posture, would influence the assessment. In this study, we specifically tested finger tapping movements which allowed us to rule out the possibility that bradykinesia in ET could be attributed to tremors, as tremors may have a greater impact on proximal arm movements [26]. In this regard, we also observed no correlation between tremor severity and finger tapping velocity in ET patients. Finally, while the level of agreement among evaluators during the blinded examination of video recordings was merely "fair", confirming previous observations [130] , the findings

obtained from the kinematic analysis were consistent with the clinical outcome. To our knowledge, this is the first study assessing bradykinesia through a blinded analysis on simultaneous video and kinematic recordings of finger tapping recordings in a broad sample of PD, ET, and HC. Our findings showed that nearly 80% of the participants were classified as bradykinetic, based on an MDS-UPDR finger tapping score of ≥ 1. However, upon further analysis, it was observed that individuals with PD exhibited more severe bradykinesia scores compared to those with ET and HC, while those with ET demonstrated higher scores than those in the HC group. Though it is not surprising that the PD group exhibited higher bradykinesia scores, our study's sample consistently displayed a greater proportion of bradykinetic ET cases than those reported in prior research, which ranged from less than 2% to 20% [24,47,144–150]. There are various factors that could account for discrepancies in findings between our study and previous research. For example, in our analysis we utilized a MDS-UPDRS score threshold of ≥ 1; additionally, it is worth noting the absence of blinding techniques during bradykinesia evaluation in earlier investigations. It is important to note that only one previous study has specifically evaluated finger tapping movements [24], which are considered the most effective test for detecting bradykinesia in clinical practice [7,13,59,133,139,140]. Also, Jimenez-Jimenez and colleagues evaluated finger tapping solely in regard to movement time, and they did not provide additional details regarding tapping performance or the prevalence of bradykinesia in those with ET as compared to HC. Our data also point to the large overlap that can exist between clinical features of PD and ET [40,41], which has led over the years to the need to introduce new diagnostic categories, such as ETPD [40] and ET-plus category [46]. Due to the lack of longitudinal evaluations, future works will clarify whether such overlapping features between the two clinical conditions represent a warning bell suggestive of a

phenoconversion from ET to PD. In our study, we also discovered that over 50% of HC had an MDSUPDRS score ≥ 1, but none of them scored higher than 2. This finding agrees with the recent suggestion that "mild parkinsonian signs" may be present in as many as 46% of otherwise healthy individuals [54,130]. The clinical results were supported by the kinematic findings, which revealed that most PD patients had bradykinesia with sequence effect and an irregular movement rhythm, whereas individuals with ET exhibited only isolated bradykinesia. These findings underscore the importance of thoroughly evaluating all movement abnormalities associated with bradykinesia, which may differ depending on the underlying etiology. As such, when dealing with bradykinesia, it is essential to deconstruct its features, identifying whether it presents in combination with hypokinesia, sequence effect, and hesitations/halts (Axis I, bradykinesia phenomenology) [12].

One additional finding of our study is the significant overlap of kinematic data, indicating that a given clinical score may reflect a diverse range of kinematic values. Thus, kinematic and clinical assessments were not always consistent, so an individual with low clinical scores (i.e., no/minimal bradykinesia) may actually have low amplitude and velocity values or an altered kinematic rhythm, and vice versa. Further analysis revealed a marked overlap of kinematic parameters among the three groups (PD, ET, and HC). To estimate the probability of being assigned to a specific clinical score group and diagnostic group based on individual kinematic parameters, we conducted ordinal and multinomial logistic regression analyses, considering both the individual kinematic parameters as well as the CKS, which aggregates various kinematic movements into a single value. Consistent with expectations, the CKS values of PD patients were found to be the highest among the three groups. We found that kinematics could differentiate between individuals with moderate/severe bradykinesia and those with normal motor function, e.g., eukinesia [12].

Additionally, both movement velocity and the CKS exhibited high specificity in distinguishing PD patients from HC. However, it was unlikely that the present methodology could correctly classify participants with intermediate kinematic values. In summary, by utilizing a combination of kinematic parameters, we were able to accurately predict with high precision whether a subject belonged to the PD or HC group. Nevertheless, approximately 30% of our sample exhibited mild to moderate kinematic abnormalities that precluded us from accurately diagnosing their condition using the methodology presented. As a result, a comprehensive evaluation and characterization of bradykinesia features, whether considered independently or in conjunction, proved inadequate in establishing the underlying etiology in all cases [12]. The present finding indicates that there can be a complex relationship between the phenomenology of bradykinesia and its etiology. In these conditions, it is crucial to evaluate other clinical symptoms and signs to achieve an accurate diagnosis. It is important to note that in our study, we specifically examined abnormalities in voluntary movement. Nonetheless, as discussed in our viewpoint, including an evaluation of spontaneous movement, as well as other symptoms could greatly improve the diagnostic accuracy [12].

It should be noticed that we only enrolled patients with mild PD and ET. Based on previous evidence, we can hypothesize patients in more advanced disease stages may display different bradykinesia features [13,16,93]. Studies in PD, for example, have shown that advanced patients do not show the sequence effect, but have a markedly reduction of movement amplitude (marked hypokinesia) [13,16]. Only one study evaluated bradykinesia in patients with ET using a longitudinal approach, showing that a similar rate of decrease in movement velocity and amplitude (brady-hypokinesia) can be observed in patients during disease progression [93]. Further studies of larger samples of patients at different disease

stages and other longitudinal works are needed to support these findings. Finally, future study will assess the possible effect of aging on bradykinesia comparison between PD, ET, and HC.

In conclusion, this study provides evidence supporting previous observations that bradykinesia can occur in conditions other than PD and demonstrates that its features vary depending on the underlying condition. Overall, the features of bradykinesia can provide valuable information for distinguishing PD from ET and healthy aging, but the interpretation should always consider the context of the individual and the presence of other symptoms or signs. Therefore, a comprehensive clinical assessment that integrates subjective and objective measures is necessary for accurate diagnosis and follow-up.

3.2 STUDY 2: Analysing the 'Bradykinesia Complex' in Parkinson's Disease

3.2.1 Introduction

Bradykinesia is the hallmark feature of parkinsonism and, according to current clinical criteria for PD, is defined by movement slowness and the sequence effect (progressive reduction in speed and/or amplitude as movements are continued) [7]. We recently proposed redefining bradykinesia as a complex of motor abnormalities with specific combinations representing separate pathophysiological elements [12]. We proposed describing the primary phenomenological features of the 'bradykinesia complex' in each subject, e.g., bradykinesia (movement slowness), hypokinesia (reduced movement amplitude), dysrhythmia (altered movement rhythm, that is movement hesitations or halts) and sequence effect [12]. Our proposal recommended the assessment of these individual features and their possible combination, hypothesizing that bradykinesia with sequence effect and/or additional motor abnormalities, strongly suggests parkinsonism [12,13]. In contrast, isolated bradykinesia and related features may be nonspecific findings, occurring across various conditions, including non-parkinsonian etiologies and healthy aging [26,28,39,54,89,90,92,151–154].

Following our paper, various studies have examined the 'bradykinesia complex' in different settings [55,92,94,155–167]. In a recent kinematic study, we examined bradykinesia features in PD patients, individuals with ET, and healthy controls [92]. The study confirmed substantial overlap in kinematic profiles across these groups, reinforcing the idea that certain motor features are not exclusive to PD, and supporting other experimental reports [26,55]. The study also indicated bradykinesia as the best distinguishing characteristic between groups [92]. Other studies assessing finger-tapping using customized smartphone

apps and typing tests, highlighted the complexity of impaired movement execution in PD [164,165]. Again, functional neuroimaging study applied the redefined bradykinesia framework to investigate the neural correlates of each motor abnormality, uncovering distinct pathophysiological mechanisms[30]. Despite the contribution of the above-mentioned studies, no previous reports have yet focused on how bradykinesia and related features specifically combine and interact in individuals with PD and in healthy subjects. Understanding the combination of bradykinesia features may help providing phenomenological insights useful in routine clinical assessment and in the accurate clinical classification of individuals [12,13,168].

In the present paper, we objectively investigate the 'bradykinesia complex' [12], in a large sample of PD patients and in healthy elderly individuals. We used a kinematic analysis system to assess the finger-tapping maneuver i.e., the most widely used task in clinical settings [7,13,92,139,140,166]. We first conducted group comparisons between PD patients and healthy controls (HCs) on kinematic variables to identify overall motor differences. Next, we applied unsupervised clustering to explore the underlying structure of the data independently of clinical labels. This analysis revealed a substantial overlap between PD patients and HCs, highlighting the heterogeneity of motor impairments and the limitations of binary classification. To further evaluate the discriminative power of each kinematic variable, we performed Receiver Operating Characteristic (ROC) curve analyses and identified optimal diagnostic cut-off values and examined how the different features combine with each other in individual cases. Also, we applied Bayesian classification to quantify the probability of PD diagnosis based on specific combinations of motor abnormalities. Regression analyses were used to examine the relationship between kinematic features and clinical variables, including treatment state and motor severity.

Finally, we evaluated the effect of dopaminergic therapy on the 'bradykinesia complex' by testing patients both ON and OFF medication.

3.2.2 Materials and Methods

Participants

We enrolled 350 subjects, including 192 patients (age range 40-85 years) diagnosed with PD according to the current diagnostic criteria [7], and 158 healthy elderly controls (HCs) matched for age and sex (details on clinicodemographic comparisons are reported in Table 3). These individuals were recruited at the Department of Human Neurosciences, Sapienza, University of Rome, Italy, and IRCCS Neuromed, Pozzilli (IS), Italy, between March 2015 and March 2024. None of the HCs had a history of neurological or psychiatric disorders, nor were they taking any medications affecting the nervous system. All patients with PD underwent one experimental session after an overnight withdrawal of their usual therapy in the case of levodopa, or 36 h or longer in the case of longer-acting agents (OFF medication state). A subset of 129 PD patients were also tested during their best treatment effect (ON medication state). HCs underwent one experimental session. All participants underwent a complete neurological examination, as well as a cognitive evaluation using the Montreal Cognitive Assessment (MoCA) [138], and a mood evaluation using Beck's Depression Inventory (BDI) scale [169]. Motor function in patients was assessed using part III of the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS-III)[139,140]. Levodopa equivalent daily dose (LEDD) was calculated for all PD patients [170]. All participants provided informed consent prior to participating in the experimental procedures. The study was approved by the local institutional review board

and conducted in compliance with international safety guidelines [171]. The study adhered to the ethical standards outlined by the Declaration of Helsinki.

Kinematic recording and analysis

We analyze the kinematics of repetitive finger-tapping using a 3D optoelectronic system (SMART motion system, BTS, Milan, Italy). This system featured three infrared cameras with a sampling rate of 120 Hz. Reflective markers, measuring 5mm in diameter and of negligible weight, were taped to the participant's hand [16,26–28,59,68,89,92,93,136,142,158,160,172,173]. Participants were comfortably seated in a chair and instructed to perform repetitive tapping of their index finger on their thumb for 15 seconds. Three consecutive trials of 15 seconds each were recorded for each hand, and the order of these trials was randomized to minimize potential biases. To prevent fatigue, a rest period of 45-60 seconds was provided between each trial, ensuring optimal performance throughout the experimental sessions [16,26–28,59,68,89,92,93,136,142,158,160,172,173]. The collected kinematic data were blindly analyzed using specialized software (SMART Analyzer, BTS, Milan, Italy). We measured the number of movements. Furthermore, we measured movement rhythm quantified by the coefficient of variation (CV) of the inter-tap intervals [16,26–28,59,68,89,92,93,136,142,158,160,172,173]. Linear regression techniques were used to determine the intercept (reflecting movement amplitude in degrees and velocity in degrees/s at the start of the 15-s motor sequence) and the slope (representing amplitude and velocity decrement, i.e., sequence effect, across the 15-s trials) of the regression line in the scatter plot of kinematic parameters (y-axis) versus the number of movements (x-axis) [16,26–28,59,68,89,92,93,136,142,158,160,172,173].

Statistical analysis

Group comparisons

Data analysis was performed using both parametric and non-parametric tests depending on data distribution. Age differences between PD and HCs were evaluated using the Mann-Whitney U test, while sex differences were assessed using Fisher's exact test. Differences in MoCA and BDI scores between patients and controls were evaluated with the Mann-Whitney U test. MDS-UPDRS (part III) scores and other clinical scale scores in patients tested during the 'OFF' and 'ON' medication states were compared using the Wilcoxon test. We compared finger-tapping kinematics between PD and HCs using unpaired t-tests and analyzed kinematic differences between PD OFF and ON conditions using paired t-tests. We assessed the normality of neurophysiological data using the Shapiro-Wilk test. Unless otherwise specified, all results are expressed as mean values ± standard deviation (SD), and the significance level for all tests was set at $p<0.05$. All data were analyzed using STATISTICA (TIBCO Software Inc., Palo Alto, California, US) and implemented with R (version 4.4.2).

Clustering analysis

To further explore data structure, we performed unsupervised clustering on kinematic data collected in the OFF-medication state using the mclust package in R (version 4.4.2), which employs Gaussian Mixture Models (GMM) for model-based clustering. The optimal number of clusters was determined using the Bayesian Information Criterion (BIC).

Receiver Operating Characteristic (ROC) curves analysis

Receiver Operating Characteristic (ROC) curves were utilized for visualization and determination of the predictive power of each kinematic variable for a diagnostic category (PD OFF vs HCs). The area under the ROC curve (AUC) served as a measure of the model's discriminative capability. To determine the optimal cut-off point, we employed the 'Closest-to-(0,1) Method', which minimizes the Euclidean distance between the ROC curve and the ideal point (0,1) on the ROC plane. This method optimally balances sensitivity (true positive rate) and specificity (true negative rate) for classification. Using these kinematic cut-off values, we categorized individuals based on specific motor abnormalities if their values exceeded or were lower than the cut-offs. This approach transformed continuous kinematic parameters into dichotomous variables. Since finger-tapping abnormalities could occur independently or in combination, we identified all possible movement categories, including normal movement (see Tables 4,5 and 7). We then counted the number of participants in each of the 16 categories across the two groups and medication states (OFF vs. ON). Fisher's exact test compared the distribution of subjects with normal vs abnormal movement between groups, while the McNemar test assessed differences between OFF and ON conditions. We used the Mann-Whitney U test and the Wilcoxon signed-rank test to evaluate differences in the number of bradykinesia features (ranging from 0= normal movement to 4 = all features present) across groups and medication states.

Bayesian classification

We applied Bayes' theorem to estimate the conditional probability of a participant belonging to the PD (OFF medication) or HCs group based on bradykinesia features combinations:

$$P(\text{Group} \mid \text{Feat Combination}) = \frac{P(\text{Feat Combination} \mid \text{Group}) * P(\text{Group})}{P(\text{Feat Combination})}$$

Where: P(Group|Feat Combination) is the probability that the individual belongs to a certain group (PD or HCs), given the specific combination of bradykinesia features; P(Feat Combination|Group) is the likelihood of observing a specific combination of features within a particular group, based on the study results; P(Group) is the prior probability of an individual being from each group, with i.e., P(PD)=0.55, P(HCs)=0.45; P(Feat Combination) is the total probability of seeing a certain bradykinesia features combination across both groups.

The same Bayesian approach was used to classify medication states in patients, with:

$$P(\text{Med State} \mid \text{Feat Combination}) = \frac{P(\text{Feat Combination} \mid \text{Med State}) * P(\text{Med State})}{P(\text{Feat Combination})}$$

with P(Med State) =0.5.

Regression analyses

We conducted multiple linear regression analyses in patients and controls to assess the predictive effect of clinical and demographic variables (sex, age, MoCA, BDI, for both groups; additionally, disease duration, LEDD, and MDS-UPDRS III OFF for the PD group) on the dependent variable (number of movement abnormalities). A similar analysis was conducted in the subsample of patients tested in the ON medication state, adding the independent variable delta MDS-UPDRS III, obtained by subtracting the MDS-UPDRS III ON medication state from the MDS-UPDRS III OFF medication state. Stepwise factor selection models were used with inclusion criterion F=0.05 and removal criterion F=0.1.

3.2.3 Results

Group comparisons

When comparing PD patients 'OFF' medication vs HCs we found lower movement velocity and amplitude values in the PD group, as well as higher CV values in PD compared to controls; the analysis also revealed differences in terms of amplitude slope, with higher values in the PD group indicating a greater sequence effect (all ps<0.001, Table 3). Conversely, number of movements and velocity slope values (which were not considered in further analysis) did not differ between groups. When comparing PD patients 'OFF' vs 'ON' medication state, we found that movement velocity and amplitude in PD were significantly higher in the ON compared to the OFF-medication state ($p \leq 0.001$, Table 1). Other kinematic parameters did not significantly change in the 'OFF' vs 'ON' medication state.

Cluster analysis

The analysis identified two clusters as the optimal solution (Figure 5, Table 4). Cluster 1 was predominantly composed of PDs, with 80 out of 98 members belonging to this group. In contrast, Cluster 2 displayed a more balanced distribution, comprising 140 HCs and 112 PD. The result confirms the visual impression of substantial overlap between patient and control data distributions, with approximately 70% of all subjects grouped together in Cluster 2 (Figure 5, Table 4).

ROC curve analysis

The diagnostic accuracy of kinematic parameters, as indicated by AUC values, was moderate, except for number of movements and velocity slope values. Among all

parameters, movement velocity emerged as the most effective discriminator between PD and HCs, with sensitivity and specificity values of 0.77 and 0.73, respectively (Figure 6, Table 5). Based on kinematic cut-off values derived from the ROC curve analysis (Table 5), nearly all patients in their OFF-medication state (186/192, 96.9%) demonstrated at least one movement abnormality. Bradykinesia was the most prevalent abnormality, and it was present in 148 out of 192 (77.7%) patients, either alone or in combination with other features. Hypokinesia and the sequence effect were also common, observed in 130 (68.5%) and 109 (61.4%) patients, respectively, while dysrhythmia was present in a lower percentage of subjects (59.2%).

Most PD patients exhibited combinations of motor abnormalities (Figure 7A, 8A; Table 6). Notably, bradykinesia frequently co-occurred with hypokinesia, while sequence effect tended to cluster with dysrhythmia. Finally, the co-occurrence of all four motor abnormalities was observed in nearly 20% of PD (Figure 7A; Table 6). Upon examining specific combinations with particular reference to current clinical criteria for PD [7], the combination of bradykinesia and sequence effect, alongside additional motor abnormalities, was present in only 79 out of 192 patients (41%). Moreover, only 5.2% exhibited bradykinesia and sequence effect in isolation (Figure 7A, Table 6).

Although lower than that observed in PD ($p<0.001$ by Fisher's exact test), a notable proportion of HCs (128/158; 81%) also exhibited finger-tapping abnormalities. In absolute terms, the most common feature in HCs were the sequence effect, present in 65 individuals (34%), followed by hypokinesia and bradykinesia, observed in 61 (31.9%) and 42 (21.7%) individuals, respectively. Dysrhythmia was observed in 32 HCs (16.7%). Notably, the number of motor abnormalities differed between patients and controls ($p<0.001$). Unlike PD

patients, most HCs exhibited only one (43%) or two (27.8%) motor abnormalities (Figure 7A, 8A; Table 6). When combinations occurred, again, the most common were bradykinesia and hypokinesia, or sequence effect plus dysrhythmia (Figure 7A, Table 6). Only 8.9% of HCs exhibited three motor abnormalities, while only 1.3% showed all four features (Figure 7A, 8A; Table 6).

The total number of patients with bradykinesia (alone or combined) decreased significantly with therapy (99/129 OFF vs. 75/129 ON, $p<0.001$). Similarly, the number of patients with hypokinesia significantly decreased (89/129 OFF vs 75/129 ON, $p<0.001$). The number of patients showing the sequence effects was slightly modified by therapy (78 OFF vs 73 ON, $p=0.03$), while the number of patients with dysrhythmia remained unchanged (73/129 OFF vs 67/129 ON, $p=0.17$). Although the overall number of patients with abnormal movement did not change (124 OFF vs 124 ON, $p=1$), we found that dopaminergic therapy significantly impacted on the number of bradykinesia features in patients ($p<0.001$ by Wilcoxon signed-rank test) (Figure 3B and 4B). However, treatment did not alter the specific combinations of motor features observed OFF medication (Figure 7B, Table 8).

Bayesian classification

We identified the motor pattern as the most distinctive for PD diagnosis: the combination of all four motor features, which yielded a 94.6% probability of PD and only a 5.4% probability of HC (Table 8, Figure 9A). The second most predictive combination consisted of bradykinesia, sequence effect, and dysrhythmia, with a 93.3% probability of PD. Other three-feature combinations, such as bradykinesia, sequence effect, and hypokinesia, or bradykinesia, hypokinesia, and dysrhythmia, both had an 83.3% probability of PD. Conversely the combination of bradykinesia and sequence effect, as for the current clinical

criteria for PD [7], had a 78.1% probability of PD. Isolated abnormalities—such as sequence effect or hypokinesia alone—were more indicative of HC, with probabilities varying across single motor features (Table 8, Figure 9A). Bayes' theorem also revealed that the presence of all four motor features indicated the OFF state (69.2% probability). Conversely, the presence of two abnormalities was more characteristic of the ON state (Table 9, Figure 9B).

We also applied the Bayes' theorem on Cluster 2, which included more than 70% of cases. Consistent with findings from the whole sample, the combination of all four motor features in Cluster 2 yielded a high probability of PD (85.7%). The combination of bradykinesia, sequence effect, and hypokinesia showed an 83.3% probability of PD, while bradykinesia, sequence effect, and dysrhythmia had only a 66.7% probability of PD. Isolated abnormalities, such as isolated sequence effect or hypokinesia alone, were again more indicative of HC (Table 10). Notably, in Cluster 2, the combination of bradykinesia and sequence effect [7] without additional motor abnormalities had no discriminatory power between patients and controls (Table 10). Details on bradykinesia features combinations in Cluster 1 are depicted in Table 11.

Regression analysis

Regression analysis in the whole PD sample revealed a statistically significant model that explained 14.8% of the variance in the number of motor abnormalities [adjusted $R^2 = 0.148$, $F(3, 187) = 12.01$, $p<0.001$]. The MDS-UPDRS III score was a moderate-to-strong positive predictor of motor impairments, demonstrating a large effect size (standardized $\beta=0.37$, $t=5.27$, $p<0.001$), i.e., clinical motor scores predict the number of bradykinesia features in patients. In contrast, MoCA scores and age were negative predictors, both with small-to-moderate effect size (MOCA: standardized $\beta=-0.16$, $t=-2.28$, $p=0.02$; age: standardized $\beta=-$

0.24, t=-3.33, p=0.001), i.e., lower MoCA scores and younger age were associated with a higher number of bradykinesia features. Other variables, including sex, BDI, disease duration, and LEDD, were excluded from the model as they did not significantly enhance its explanatory power. In the ON medication state subgroup, LEDD was another negative predictor of motor impairment, with moderate-to-strong effect size (standardized β=-0.30, t=-3.16, p=0.002), i.e., lower LEDD were associated with a higher number of bradykinesia features. Further details of this analysis are included in Table 12. Finally, in the HCs group, no regression model was established, indicating that none of the independent variables predicted the number of bradykinesia features.

3.2.4 Discussion

Our study represents the most comprehensive kinematic investigation of bradykinesia and related features in a large cohort of PD patients and elderly controls conducted to date. Namely, we objectively examined the 'bradykinesia complex' concept. Bradykinesia—defined as slowness of movement—emerged as the most prevalent motor abnormality in PD patients and the most accurate feature for distinguishing them from HCs, despite substantial variability and overlap in other kinematic measures. Notably, the discriminatory power of bradykinesia increased significantly when combined with other motor features such as hypokinesia, dysrhythmia, and the sequence effect. In contrast to patients, HCs typically exhibited isolated motor alterations. Lastly, dopaminergic treatment produced differential effects on bradykinesia and its associated features in patients. Overall, our findings provide objective insights into the 'bradykinesia complex' and may have important implications for understanding its pathophysiology in both PD patients and healthy elderly individuals.

Insights into the concept of the 'bradykinesia complex'

The key finding of this study is the objective demonstration that, despite a significant overlap between patient and control data, most patients with PD exhibited multiple concurrent motor abnormalities, whereas most HCs showed isolated abnormalities. Using a Bayesian approach, we demonstrated that the combination of bradykinesia, hypokinesia, dysrhythmia, and the sequence effect was associated with a 94.6% a priori probability of PD, compared to only a 5.4% probability of being an HC. Notably, other frequent combinations of three motor abnormalities in PD included: (i) bradykinesia, hypokinesia, and dysrhythmia; (ii) bradykinesia, dysrhythmia, and the sequence effect; and (iii) bradykinesia, hypokinesia, and the sequence effect, each associated with an a priori PD probability ranging from 83% to 93%. Less commonly, PD patients presented with only two motor abnormalities. In these cases, two main patterns emerged: (i) bradykinesia combined with hypokinesia, and (ii) the sequence effect combined with dysrhythmia. These findings, beyond offering insights into the concept of the 'bradykinesia complex,' may also be interpreted considering both the quantitative, i.e. the number, and the qualitative nature of the combinations observed. Further considerations specifically pertain to the findings in healthy individuals.

Regarding the significance of the number of motor abnormality combinations observed in patients, our regression analysis showed that a higher number of motor abnormalities was associated with higher clinical motor scores. This suggests that individuals with a more complex combination of bradykinesia and related feature tend to exhibit a more severe clinical picture. Accordingly, we observed that the number of bradykinesia features predicted lower cognitive scores, in line with previous findings [89,158,172]. Interestingly,

the number of bradykinesia features in individual patients did not correlate with disease duration, indicating that the extent of impairment within the 'bradykinesia complex' is not merely a consequence of disease progression. This interpretation is further supported by the lack of correlation between the number of bradykinesia features and age. In fact, age emerged as a negative predictor of the number of abnormalities, meaning that younger patients in our cohort were more likely to present with a greater number of bradykinesia features. Overall, these findings allow the hypothesis that PD subtypes may be independent of disease duration, and may be driven by different underlying pathophysiological mechanisms.

Concerning the qualitative of bradykinesia features combination, the observation of bradykinesia and sequence effect, as specified by the MDS consensus criteria [7], was relatively low among patients, especially when compared to other types of motor feature combinations. Again, the sequence effect may be absent in a substantial proportion of patients. These observations confirm previous findings from smaller cohorts [13,16,92] and calls into question the current definition of bradykinesia [7]. In this context, the term "bradykinesia and associated features" [12] appears more appropriate than "bradykinesia and sequence effect," as it better reflects the heterogeneous spectrum of motor abnormalities observed in PD.

The identification of heterogeneous motor patterns in Parkinson's disease, with at least two distinguishable subgroups—one dominated by bradykinesia and hypokinesia, and another characterized by rhythm disturbances and the presence of the sequence effect—supports the hypothesis that different motor phenotypes may represent clinically and biologically meaningful subtypes of the disease. These differences appear to reflect partially distinct

pathophysiological mechanisms: while bradykinesia and hypokinesia have consistently been associated with dopaminergic denervation of the dorsal striatum and dysfunction within basal ganglia–thalamo–cortical loops [57,66,67], reduced pre-SMA activation has been linked to the inability to maintain stable motor output over time, clinically manifesting as the sequence effect. Conversely, dysrhythmia may reflect alterations in internal timing processes, potentially mediated by abnormal cerebello–thalamo–cortical connectivity[13]. These different clinical manifestations may therefore reflect a heterogeneous involvement of distinct nodes within the bradykinesia network, varying across patients with PD.

Regarding observations in the elderly population, it is important to recognize that motor abnormalities are not exclusive to PD but can also be present in healthy aging individuals, albeit often in a different form and pattern. We observed that a substantial number of HCs also exhibit motor abnormalities [55,145,174,175] —typically as isolated manifestations within this subgroup—raising important considerations regarding the natural variability of motor function in aging populations and the potential overlap between normal age-related motor decline and PD. Previous clinical and experimental studies have demonstrated that mild parkinsonian signs (MPS), including subtle bradykinesia, may occur in up to 30–40% of otherwise healthy elderly individuals [7,54,55,92,154]. Although their clinical significance remains somewhat unclear, the presence of MPS in older adults has been interpreted as a potential early indicator of underlying neurodegenerative changes [54,154,176–179]. Longitudinal studies have linked MPS to a higher risk of developing PD, cognitive decline, and other neurodegenerative diseases [151,174,176,180–182]. Neuroimaging has confirmed structural and functional alterations in motor-related regions and dopaminergic pathways in individuals with MPS [151,174,176,182,183]. Beyond the dopaminergic system, other neural circuits also play a significant role in the motor disturbances observed with aging. One

critical system involved is the cholinergic system, which is essential for motor coordination, cognitive function, and overall neural regulation. Acetylcholine modulates the activity of both the motor cortex and the basal ganglia, interacting with cortico-striatal circuits to influence dopaminergic transmission and, consequently, movement execution [55,89,172,184]. Neuroimaging studies have shown a reduction in cholinergic innervation, particularly in the basal nucleus of Meynert, which correlates with both motor and cognitive deficits [185]. An additional intriguing finding is the high prevalence of an isolated sequence effect in healthy elderly individuals. Hence, isolated sequence effect may represent a specific form of MPS associated with aging or may be non-specific, as healthy individuals maintain normal movement amplitudes at the beginning of the sequence—unlike PD patients, who exhibit marked hypokinesia [16]. These findings suggest that the sequence effect, by itself, may represent a nonspecific phenomenon that can also be observed to some extent in healthy elderly individuals. This raises important questions about its diagnostic specificity and indicates that the sequence effect alone might not be a definitive marker of PD, but rather part of a broader spectrum of age-related motor changes. This issue, however, warrants further investigation.

Pathophysiological implications

The study results may be interpreted from the pathophysiological standpoint and supports the hypothesis of bradykinesia as a network disorder, caused by dysfunction in multiple brain regions rather than the failure of a single system [12,13,90]. In this framework, each bradykinesia feature may reflect the differential involvement of specific nodes within this network, which includes not only the basal ganglia but also the sensorimotor cortical areas and the cerebellum [12,13,90]. Moreover, it can be hypothesised that certain alterations tend

to co-occur preferentially coexist in patients because they are linked to similar pathophysiological mechanisms, e.g., bradykinesia and hypokinesia arise from mechanisms distinct from those underlying the sequence effect and dysrhythmia [16,59,76,141,186–189]. Alternatively, their co-presence might be explained by biomechanical principles, given that movement speed is typically proportional to movement amplitude under normal conditions—a relationship that can be altered in PD [136,190]. The effect of dopaminergic medications on each feature could also be interpreted from a pathophysiological standpoint. Notably, we observed that therapy improves bradykinesia and hypokinesia but has little effect on dysrhythmia or the sequence effect [59,136,141,160,162,188]. It is possible that these two specific alterations are less sensitive to dopamine because they are not solely dependent on dopaminergic loss. Supporting this, previous studies have shown that bradykinesia, hypokinesia, and the sequence effect exhibit variable sensitivity even to surgical interventions, likely due to the multilevel network effects of such treatments [13,59,191]. Moreover, the different characteristics of bradykinesia respond differently to various types of stimulation, such as high- or low-frequency deep brain stimulation [192]. The clustering observed may not simply reflect random variability, but may represent a first step towards a potentially different stratification of PD into recognizable subtypes based on objective quantitative parameters. Although the study does not include structural, functional, or genetic biomarkers, the identification of these distinct patterns through markerless methods and kinematic analysis suggests that these tools could contribute to the phenotypic characterization of the disease in a non-invasive way. This aspect is of growing importance, especially from a personalized medicine perspective: the early identification of PD subtypes could support the choice of targeted treatments, improve the prediction of clinical progression, and guide future studies on new therapeutic targets [193]. Finally,

neurophysiological and neuroimaging studies have highlighted pathophysiological differences between PD patients with and without the sequence effect, particularly in cortical and cerebellar regions [12,13,64,76].

Confounds and study limitations

Given the demographic similarities between the PD and HCs groups, we exclude these factors as potential confounders. PD diagnosis was based on clinical criteria, and although not all patients underwent dopamine transporter (DAT) SPECT, consistent long-term monitoring minimized misdiagnosis bias [7,133]. Moreover, we did not perform a DAT SCAN in HCs, as there was no clinical indication. To assess bradykinesia, we utilized finger-tapping movements, the most valuable task in clinical practice [7,12,13,59,90,140] [2–4,32,33,40]. Notably, we have used an experimental approach that has been thoroughly validated in several prior studies [16,26–28,59,68,92,93,142,172,194]. However, we did not investigate bradykinesia features during other task, nor in other body regions, with potentially different characteristics [76,80,195]. Again, we here only focused on voluntary movements, and have not considered alterations in spontaneous movements, i.e. oligokinesia [12], as this aspect was beyond the scope of the project. We tested patients both under their usual dopaminergic therapy and after they discontinued the medications prior to the experimental evaluation. This approach minimized the potential confounding effects of antiparkinsonian drugs on the assessment of kinematic variables. Finally, we ensured that the researchers who performed kinematic analyses were blinded to the participants' diagnosis (PD vs HCs) and to the experimental condition (ON' vs 'OFF' condition), minimizing this potential bias. Despite the large sample of subjects studied, some of the 16 a-priori categories included a limited number of individuals, which may make the results of

the Bayesian analysis less reliable. Other potential limitations of the study include the focus on PD patients in the intermediate phase and the absence of a longitudinal design, both of which could be addressed in future research.

3.2.5 Conclusions

This study provides new insights into the 'bradykinesia complex' and highlights the challenges of evaluating its full spectrum in both clinical and research settings. Diagnostic accuracy improved when multiple motor abnormalities were considered together, emphasizing the importance of assessing the complete range of bradykinesia and related features. Our findings also show that different components of bradykinesia vary in their response to pharmacological treatment, supporting the view that bradykinesia arises from dysfunction across multiple brain regions. Clinically, this underscores the heterogeneity of PD and suggests that detailed motor phenotyping could be valuable in routine patient evaluations. This approach may have therapeutic implications, as some motor patterns respond differently to dopaminergic therapy. Although lower dopaminergic doses (LEDD) were associated with fewer motor abnormalities, changes in overall clinical scores (MDS-UPDRS III) did not predict the number of abnormalities, reflecting the complex and feature-specific effects of treatment. Future research, possibly complemented by neurophysiological and neuroimaging methods, is essential to further unravel the intricate pathophysiological mechanisms underlying the 'bradykinesia complex' and to refine PD diagnostic criteria accordingly.

3.3 STUDY 3: Validation of Computer Vision Techniques for Movement Analysis: Clinical Perspectives

3.3.1 Introduction

Movement disorders constitute a heterogeneous group of neurological conditions characterized by qualitative and quantitative alterations in voluntary and involuntary motor activity. Clinically, movement disorders can be distinguished into hyperkinetic forms, characterized by excessive motor activity such as tremor, dystonia, chorea, myoclonus and tics, and hypokinetic forms, in which bradykinesia and rigidity prevail, typical of PD, atypical parkinsonisms and secondary parkinsonisms [196]. Underlying this is usually a dysfunction of the basal ganglia, subcortical structures involved in motor control, procedural learning, executive functions and the regulation of emotional responses [197,198]. One of the most studied symptoms of movement analysis in neurological disorders is bradykinesia [13,16,92]. Typical of hypokinetic forms such as PD, bradykinesia manifests as slowness in the initiation and execution of voluntary movements, associated with reduced amplitude and speed in repetitive movements (sequence effect)[7,12]. Clinical assessment traditionally relies on direct observation and standardized scales, such as the MDS-UPDRS [139,140]. However, these instruments show significant limitations, related to the subjectivity of clinical assessment, high intra- and inter-observer variability and low sensitivity in detecting subtle changes over time [92,119]. Instrumental techniques based on quantitative measurements such as motion capture systems, accelerometry and surface electromyography have improved the accuracy of assessment, but their use is hindered by high costs, low accessibility and the need for experienced personnel. In the research field, the most widely used tools for the kinematic analysis of motor disturbances are

optoelectronic systems with infrared cameras, which, in combination with reflective markers applied to the body segments, allow an accurate three-dimensional reconstruction of movement [16,59,92,94,136,199].

In recent years, CoV has opened up new perspectives in the quantitative assessment of movement disorders. In particular, markerless pose estimation techniques make it possible to extract accurate kinematic data from simple videos, even recorded with commonly used devices such as smartphones or tablets [108,200,201]. Several studies have confirmed their reliability and reproducibility, demonstrating high concordance with accelerometry even for symptoms such as tremor [108,200]. In the light of these results, the same technology has been extended to the study of bradykinesia, through the use of open-source frameworks such as *MediaPipe* or *Vision*, which allow real-time automated analysis without the need for specialized instrumentation. The results obtained show a solid correspondence with those derived from conventional clinical instruments. In this context, particular attention was paid to the finger tapping, a standard test for assessing bradykinesia, which involves rapid, repetitive movements between the thumb and index finger [202,203]. Video analysis, combined with CoV, allows the objective measurement of kinematic parameters such as angular velocity, frequency, asymmetry, amplitude over time and reaction time, overcoming the limitations of subjective observation and offering the possibility of continuous monitoring, which is also useful for assessing therapeutic efficacy, in home environments too [204–206].

The aim of the present study was to analyze the validity and clinical applicability of an open-source CoV framework, i.e. *MediaPipe* for the assessment of bradykinesia. The analysis was conducted by means of a direct comparison between the measurements obtained with *MediaPipe* and those derived from an kinematic system based on infrared cameras and

reflective markers. The objective was not only to verify the concordance between the two systems in terms of reliability and accuracy, but also to assess their concrete applicability in clinical practice, with particular attention to the simplicity of use, contained costs and the possibility of using them even in settings without advanced technology or qualified specialists. This approach is part of a broader perspective of digitization of neurology, oriented towards the development of agile, reproducible and integrable diagnostic tools in the daily assessment of patients with movement disorders.

3.3.2 Materials and Methods

Participants

To carry out the study, 17 healthy volunteers were enrolled, selected through spontaneous recruitment among university students and healthcare personnel of the Department of Human Neuroscience of the Sapienza University of Rome.

The sample consisted of eight female and nine male subjects, with a mean age of 28.41 ± 2.06 years. All participants were in good general health at the time of inclusion. Exclusion criteria included: a known history of neurological or psychiatric disease; chronic or recent intake of drugs that can interfere with motor performance (e.g. psychotropic drugs, anti-epileptic drugs, muscle relaxants); musculoskeletal pathologies affecting the upper limbs; any previous experience of professional or sports training aimed at developing manual dexterity (e.g. musicians, pianists, jugglers, conjurers, etc.), in order to avoid bias linked to specific training of fine hand movements. All participants received detailed information on the purpose of the study and how the tests were performed, and provided written informed consent prior to inclusion. The study was approved by the local ethics committee and conducted in accordance with the principles of the Declaration of Helsinki.

Computer vision (CoV)

For the purpose of the CoV analysis, each participant was positioned in a sitting position, perpendicular to the examiner, facing a uniform white background in order to optimize visual contrast and reduce visual background interference. The subject was instructed to raise the dominant arm to shoulder height, keeping the elbow flexed at approximately 90° and the hand in an intrarotation position, with thumb and forefinger initially close together. In order to standardize the distance between the acquisition device and the upper limb, a marker of negligible size (not interfering with the analysis of the gesture) was applied at the level of the second metacarpal, at the back of the hand (Figure 10). This allowed a stable reference point to be obtained for the calculation of the hand-camera distance by the processing software. The examiner, positioned behind the participant in order not to interfere with the field of view of the recording, performed the video acquisition by means of a mobile device, held freehanded in a frontal position with respect to the subject. Video acquisition was performed using the standard video mode of an iPhone 13 (Apple Inc.), recording in 1080p HD at 30 fps. The device features a dual rear camera system (12 MP wide: f/1.6; 12 MP ultra-wide: f/2.4, 120° FoV) and sensor-shift optical image stabilization. Standard video recordings were acquired simultaneously with kinematic recordings. Three consecutive videos, each lasting approximately 15 seconds, were recorded for each participant. During each trial, the subject was asked to perform the finger tapping movement of the dominant hand at the highest possible speed and amplitude, repetitively and continuously, without pause. Subsequently, the captured videos were converted to MP4 format using an online file conversion platform to ensure compatibility with the analysis software used. The analysis was conducted using a program developed in the *Python*

language [207]. The videos were processed using a CoV pipeline with several successive steps. First, the video files were loaded and decomposed into individual frames using the *OpenCV* library [208] . Each frame was then converted to greyscale and, where necessary, resized to ensure uniformity in the analysis phase. In order to detect and monitor finger movement over time, pose estimation and keypoint tracking algorithms were adopted, in particular through the use of pre-trained models such as *MediaPipe Hands* [209–212] , which allow the precise recognition of finger joints even in uncontrolled contexts. Once the finger positions in individual frames were identified, relevant temporal and spatial features were extracted, such as the distance between thumb and index finger or the frequency of tapping movements. This information was then used to quantify the number of movements, speed and amplitude during each trial. For the quantitative analysis, a data processing module was implemented that aggregated the frame-by-frame information, calculating metrics such as the average speed of tapping, the amplitude of the movement performed, and the number of movements. Extracted metrics were exported in tabular format for subsequent statistical processing.

Kinematic Analysis

The kinematic recordings were performed by means of an optoelectronic motion capture system (SMART Motion System, BTS Engineering, Italy), consisting of three infrared cameras operating at a frequency of 120 Hz. The system allows the three-dimensional tracking of movements through the acquisition of the position of reflective markers applied on the body segments of interest. The kinematic variables of position, velocity and acceleration were derived from the acquired raw data, in accordance with the principles of optoelectronic *motion analysis*. To define a local reference system of the hand and isolate the

motion of interest, reflective markers were placed at specific points: one on the tip of the index finger and one on the tip of the thumb, in order to detect the relative motion between the two fingers. A further three markers were placed on the back of the hand, on the head of the second metacarpal bone, at the base of the second metacarpal bone and at the base of the fifth metacarpal bone, respectively, in order to construct a reference plane to compensate for the possible contamination of any wrist or hand movements (Figure 10). Participants were invited to sit in a chair and were instructed to repeatedly tap the index finger of the dominant hand on the thumb for 15 seconds, at the highest possible speed and amplitude, while being video-recorded. Each subject completed three consecutive trials, interspersed with short pauses [16,59,92,194]. Once the three-dimensional coordinates were obtained from the motion capture system, it was possible to calculate trajectories, angular magnitudes, velocities and accelerations, allowing a detailed analysis of the kinematics of the body segments equipped with markers. The analysis of finger tapping was conducted using specific software (SMART Analyzer, BTS Engineering, Italy) and capable of defining the kinematic variables of interest, The kinematic variables of interest included movement amplitude (mm), speed (mm/s), total number of taps, and temporal characteristics of the repetitive finger movements. Movement rhythm was quantified using the coefficient of variation (CV) of inter-tap intervals, calculated as the ratio between the standard deviation and the mean; higher CV values indicated reduced regularity of movement execution. To assess temporal changes over the 15-second trials, linear regression analyses were performed by plotting kinematic parameters (amplitude and speed, Y-axis) against the tap sequence (X-axis). The regression intercept was interpreted as a measure of overall motor impairment (bradykinesia and hypokinesia), while the slope captured the presence and extent of the sequence effect over time [16,92,136].

Statistical analysis

To compare the two methods analyzed, the two-tailed t-test was used for paired samples in cases where the data distribution was normal; otherwise, the Wilcoxon test was applied for non-parametric data. The linear association between the measurements obtained with the two systems (2D and 3D) was assessed by means of Pearson's correlation coefficient (r) or, alternatively, Spearman's coefficient if the assumption of normality was not met. The values obtained were corrected for multiple comparisons using Bonferroni's method [213]. The agreement between the two methods was subsequently analyzed by means of Bland-Altman diagrams, which show the mean bias (bias line), limits of agreement (±1.96 standard deviations) and relative confidence bands (95% CI). The absolute agreement between the two acquisition modes was also estimated by means of the Intraclass Correlation Coefficient (ICC), calculated according to a two-way mixed-effects model, type 3,k. The ICC value, the 95% confidence interval, the F-value and the relative p-value were reported. The interpretation of the coefficient followed the criteria proposed by Cicchetti: excellent agreement for ICC ≥ 0.75; good between 0.60 and 0.74; moderate between 0.40 and 0.59; poor for values < 0.40. The level of statistical significance was set at $p < 0.05$. Unless otherwise stated, results are expressed as mean ± standard deviation (SD). Statistical analyses were performed with IBM SPSS Statistics software.®

3.3.3 Results

Table 13 shows the mean values and standard deviations of the variables considered. No statistically significant differences emerged for any of the variables considered (all $p > 0.05$), with the exception of regularity of movement and amplitude, for which significant

differences were observed ($p < 0.001$ and $p = 0.002$, respectively). These differences remained significant even after correction for multiple comparisons. The analyses showed a statistically significant correlation for the number of movements ($r = 0.971$; $p < 0.001$), for the decrease in amplitude ($r = 0.800$; $p < 0.001$) and for speed ($r = 0.795$; $p < 0.001$) (Figure 11). The decrease in speed showed a moderate but non-significant correlation ($r = 0.472$; $p = 0.05$). No significant correlation emerged for amplitude ($r = 0.371$; $p = 0.143$) and CV ($r = -0.130$; $p = 0.619$) (Figure 11). The concordance analysis between the 2D and 3D kinematic reconstruction showed a high degree of overlap between the two methods (Figure 12). The mean bias was clinically negligible for all analyzed parameters: -1.5 movements for number of movements, +0.16 for CV, +8.0° for amplitude, +0.008° for amplitude decrease, +83.8°/s for velocity, and -1.42°/s for velocity decrease. The limits of concordance (mean ± 1.96 SD) lie between -11.0 and +8.0 movements for the number of movements, -0.05 and +0.37 for regularity, -9.2 and +25.2° for amplitude, -0.20 and +0.21° for amplitude decrease, -394 and +561°/s for velocity, and -11.0 and +8.1°/s for velocity decrease, respectively (Figure 12). The absence of systematic patterns in the graphs confirms that the differences between the methods do not depend on the magnitude of the measurement, thus supporting the validity of the 2D method as a possible alternative to 3D reconstruction under the experimental conditions adopted. The ICC values showed excellent agreement for the number of movements (ICC = 0.97; 95% CI: 0.92-0.99; $p < 0.001$), and good-excellent for the amplitude decrease (°) (ICC = 0.89; 95% CI: 0.69-0.96; $p < 0.001$). Velocity (°/s) showed good agreement (ICC = 0.85; 95% CI: 0.58-0.95; $p < 0.001$), while velocity decrement (°/s) reached a moderate level of agreement (ICC = 0.64; 95% CI: 0.01-0.87; $p = 0.024$). Amplitude (°) presented moderate-poor agreement (ICC = 0.53; 95% CI: -0.31-0.83; $p = 0.073$), and regularity of movement showed poor agreement (ICC = 0.10; 95% CI: -1.49-0.67; $p = 0.421$). Overall, the

results indicate that the number of movements, velocity, velocity decrement and amplitude decrement can be measured with high reliability by both methods, making them potentially interchangeable in clinical settings. In contrast, the regularity of movement and, to a lesser extent, amplitude, do not reach sufficient levels of agreement to ensure substitutability between the two techniques.

3.3.4 Discussion

In recent years, there has been an increasing diffusion of methods based on CoV technologies, in particular markerless, for the quantitative analysis of movement in the neurological field. These tools are proving promising in providing objective, non-invasive and affordable measurements, even outside structured clinical settings, such as in home assessment. However, important methodological challenges remain and require rigorous validation through direct comparison with optoelectronic systems, considered the gold standard for three-dimensional kinematic motion analysis [92]. In the present study, conducted on 17 healthy subjects, the effectiveness of markerless CoV techniques in the quantitative analysis of repetitive finger tapping movements was evaluated, with particular reference to the finger tapping test, commonly used for the assessment of bradykinesia. The collected data were processed both by means of an optoelectronic 3D kinematic analysis system [92,199], and by means of an open-source CoV framework applied to videos recorded with a common mobile device. The results obtained showed a high correlation between the two systems for the main kinematic variables analyzed: number of movements, amplitude decrease, and angular velocity decrease, in line with previous evidence [97,214] . However, no statistically significant correlation emerged for absolute amplitude and coefficient of variation. These differences could be attributed to methodological differences.

As far as the amplitude is concerned, this discrepancy could be due to the positioning of the reference axes: in CoV, the axes are defined within a two-dimensional space on the basis of video processing, whereas in the optoelectronic system they are reconstructed in a three-dimensional context by means of markers and infrared cameras. This difference in the spatial reference system can affect the accuracy in measuring the amplitude of movements and contribute to the observed variability. As far as the coefficient of variation is concerned, an additional critical factor is the acquisition frequency: in optoelectronic systems it can vary from 100 to 2000 fps, depending on the technical characteristics (cameras, sensors, software), while in videos analyzed with CoV it is generally between 30 and 60 fps, depending on the quality of the video and the configuration of the algorithm. This discrepancy in temporal resolution may compromise the precise identification of kinematic peaks, affecting the estimation of motion variability. This aspect could explain the differences in coefficient of variation values found in the present study. In spite of the absence of statistical significance, a visual analysis of the scatter plots constructed on the data from both methods revealed a potential tendency of correspondence also for the amplitude and coefficient of variation parameters. This finding was further corroborated by analysis using BlandAltman plots, which showed a high degree of data overlap between the two systems, with a negligible average bias even for the parameters in question.

Despite the promising results achieved using markerless CoV techniques, it is essential to highlight some methodological and practical limitations. First, inter-subject variability represents a significant challenge: individual differences in body morphology, movement amplitude, and speed can affect the accuracy of anatomical landmark tracking, especially in the absence of physical markers. Furthermore, environmental conditions such as lighting, background, and camera angle may compromise the quality of video segmentation and the

temporal consistency of the signal. These factors are particularly critical in home-based telemedicine contexts, where acquisition conditions are not standardized. Another limitation is the current lack of universally accepted protocols regarding the criteria for configuring the processing algorithm, how to identify peaks (e.g., angular maxima, amplitude of movement), and video pre-processing techniques (e.g., filtering, temporal normalization), but also camera positioning, acquisition duration, and types of motor tasks to be analyzed. This delays both the comparability of studies and the replicability of results. Therefore, the future development and dissemination of operational guidelines and international standards will be crucial to support the homogeneous adoption of markerless technologies in both clinical practice and research.

The present study has some limitations such as the small sample size and the inclusion of only healthy young subjects. For a more extensive evaluation of the reliability and clinical applicability of CoV, it will be crucial to extend the trial to patients with movement disorders (e.g. PD and parkinsonisms, ET, dystonia) and to test the technology on a wider range of motor tasks, such as pronation/supination, foot tapping or walking. Furthermore, although the optoelectronic system was used as a gold standard reference, it is not free from potential inaccuracies related to calibration, marker positioning and tracking quality.

3.3.5 Conclusions and Future Perspectives

These results are part of an expanding research context that highlights the potential of CoV for the automated identification of pathological motor patterns in patients with neurological disorders. Vignoud et al. highlighted how automated analysis of bradykinesia using CoV can achieve an accuracy superimposed on traditional clinical assessment, with good levels of sensitivity and specificity [215] . The absence of markers, the possibility of using widely

available devices and the application even by non-expert personnel make CoV an ideal technology for telemonitoring and large-scale assessments. The use of CoV in finger tapping testing could allow longitudinal assessment of bradykinesia even outside the clinical setting, with potential implications in personalizing therapies. The main advantages of CoV also include rapid data acquisition and analysis, non-invasiveness and the possibility of performing objective assessments even remotely [111,216]. Moreover, integration with artificial intelligence algorithms, in particular convolutional neural networks (CNNs), has already demonstrated accuracies of over 75% in the recognition of bradykinesia and dyskinesias [111,217,218]. These developments open up the possibility of using CoV for longitudinal monitoring of symptoms and personalized optimization of treatments.

In conclusion, CoV represents an emerging technology with revolutionary potential in the objective assessment of movement disorders. The results obtained, together with the evidence in the literature, confirm its accuracy and flexibility, making it an ideal candidate for future clinical, home and research applications [111].

4. PATHOPHYSIOLOGICAL IMPLICATIONS

The methodological framework adopted in this thesis enabled a novel investigation of the pathophysiological underpinnings of bradykinesia, moving beyond its conventional characterization as mere motor slowness [7]. By integrating kinematic analysis, standardized clinical assessment, and markerless CoV technologies, it was possible to deconstruct bradykinesia into its core components—slowness (bradykinesia sensu stricto), hypokinesia (reduced amplitude), rhythm irregularity (dysrhythmia), and the sequence effect—and to evaluate their distribution, co-occurrence, and diagnostic relevance across distinct clinical populations, including patients with PD, ET, and age-matched healthy controls [13,26,55,92].

The findings substantially reinforce and expand upon the concept of the bradykinesia complex [12], suggesting that bradykinesia should be reframed as a multicomponent motor phenotype with distinct neural substrates, differential pharmacological sensitivity, and potential diagnostic specificity. In the first experimental study, although kinematic abnormalities were detectable across all groups, the most severely impaired motor profile—defined by the concurrent presence of reduced movement velocity, increased variability of inter-tap intervals, and a progressive decrement in amplitude and/or speed (sequence effect)—was predominantly expressed in the PD cohort. In contrast, individuals with ET and healthy older adults typically exhibited isolated slowness without accompanying decrement or rhythm alterations, indicating that the simultaneous expression of multiple kinematic deficits may serve as a marker of more profound disruption of cortico-basal ganglia circuitry, consistent with a parkinsonian pathophysiology.

From a systems neuroscience perspective, these observations support the hypothesis that the constituent features of bradykinesia reflect dysfunctions across distinct neural networks [12,13]. Slowness and hypokinesia have been consistently linked to dopaminergic denervation of the dorsal striatum and altered activity in the direct and indirect basal ganglia-thalamocortical loops [57,66,67]. However, the persistence of both the sequence effect and dysrhythmia in patients undergoing optimized dopaminergic therapy suggests the involvement of non-dopaminergic circuits. In particular, the pre-supplementary motor area (pre-SMA), cerebellum, and cingulate motor areas have been implicated in the temporal organization and internal pacing of repetitive motor output [59,76].

These results are in line with functional neuroimaging and electrophysiological studies showing aberrant activation patterns in both cortical and subcortical areas involved in motor

planning and sequence generation in PD. In particular, impaired pre-SMA activation has been associated with deficits in maintaining stable motor output across time, which clinically manifests as the sequence effect during repetitive motor tasks such as finger tapping. Dysrhythmia, as quantified by the CV of inter-tap intervals (RhythmK), may reflect dysfunction in internal regularity mechanisms, potentially mediated by altered cerebello-thalamo-cortical connectivity [13].

In the second study, unsupervised machine learning methods (k-means clustering) and Bayesian probabilistic modeling demonstrated that the diagnostic likelihood of PD increased monotonically with the number of abnormal kinematic components. The concurrent presence of all four core features of the bradykinesia complex was associated with a posterior diagnostic probability exceeding 95%, underscoring their clinical discriminability and their value as proxies of systemic motor circuit dysfunction. Nevertheless, a subset of participants exhibited patterns that were less readily classifiable, potentially reflecting either prodromal states or hybrid phenotypes with overlapping pathophysiological substrates [94,219].

Another relevant finding concerns the influence of aging in modulating the expression of bradykinetic motor features. Recent data suggest that motor slowing in neurologically intact elderly individuals may be associated with increased temporal variability and represent an early biomarker of functional vulnerability [54,179]. In the study of De Riggi et al., over 50% of healthy older adults exhibited scores ≥1 on the MDS-UPDRS Part III finger tapping item, despite minimal or absent dysrhythmia and sequence effect [55]. These findings are consistent with the hypothesis that physiological aging—and particularly biological frailty—

may induce a form of non-pathological motor slowing which nonetheless phenotypically overlaps with prodromal PD.

In the third study, the construct and concurrent validity of markerless motion capture systems based on CoV algorithms was examined. The extracted kinematic parameters showed strong correlation with gold-standard optoelectronic motion capture system, supporting the use of CoV as a reliable, scalable, and a non-invasive method for quantifying movement abnormalities. From a pathophysiological standpoint, this approach enables objective, reproducible quantification of each motor subcomponent, facilitates fine-grained tracking of disease progression, and offers potential for early detection of clinically silent motor deterioration .

Collectively, these findings yield several key pathophysiological implications:

1. They confirm the complexity of bradykinesia in PD and its distinction from age-related motor slowing.
2. They suggest that each feature (slowness, hypokinesia, sequential effect, and dysrhythmia) is likely supported by distinct neural circuits with varying degrees of dopaminergic sensitivity.
3. They demonstrate that isolated motor slowness has no diagnostic specificity and must be interpreted in the context of associated kinematic features.
4. They support the implementation of kinematic and CoV-based analyses as advanced diagnostic tools capable of defining disease-specific motor phenotypes and providing information on pathophysiological and prognostic subclassification.

5. GENERAL CONCLUSIONS

This thesis highlights the potential of CoV and AI-based motion analysis as transformative tools in the clinical evaluation of bradykinesia. It promotes a shift from subjective, descriptive assessments to quantitative and multidimensional models. By integrating clinical rating scales, kinematic analysis, and markerless CoV systems, the study offers a detailed characterization of bradykinesia in PD, ET, and healthy aging. The three experimental studies support the concept of a "bradykinesia complex" as a robust clinical and neurobiological construct. Remarkably, motor slowness alone is insufficient for differential diagnosis, whereas the combination of multiple movement abnormalities such as slowness, sequence effect, and irregularity of rhythm has emerged as a specific kinematic feature of PD.

Quantitative motor analysis should therefore be considered a fundamental element of precision medicine in movement disorders. Its integration into automated diagnostic tools could improve early diagnosis and personalized assessment of disease risk, particularly in the prodromal stages. The validation of markerless CoV systems—as part of the project "Telemedicine methods in the assessment of Parkinson's patients to reduce travel to outpatient clinics and protect the environment" – co-funded by the Programma Operativo Nazionale Ricerca e Innovazione (Azione IV.5 "Dottorati su tematiche Green") — demonstrates their accuracy, accessibility, and scalability in both clinical and home settings. These systems offer a possible path towards sustainable telemonitoring and continuous assessment in real life.

The adoption of such technologies is very promising for the advancement of telemedicine, enabling objective and long-term monitoring of patients in the home environment. Their affordability and ease of implementation can help reduce the burden of in-person visits,

improve access to care, and support the sustainability of healthcare systems [220,221], also through the use of commonly available technologies such as webcams and laptops. Among future directions, particular attention will be devoted to evaluating the clinical applicability of these methodologies in PD, particularly in the context of personalized telemonitoring and teletreatment systems [222]. In this context, preliminary analyses on the data collected within the framework of this research project are already in progress. However, despite encouraging initial findings, the results remain too preliminary to warrant formal publication at this stage.

Future longitudinal studies are also needed to assess the prognostic relevance of long-term kinematic biomarkers. Multimodal approaches combining clinical, neuropsychological, and instrumental data, utilizing advanced neural networks, could further improve diagnostic and therapeutic strategies. Ultimately, this work lays the foundation for a future in which bradykinesia will be objectively measured, phenotypically subclassified, and precisely treated.

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7. TABLES

Table 1: Participants' demographic and clinical features

	PD (n= 44)	ET (n= 69)	HCs (n= 77)
Gender	17 F (38.6%)	31 F (44.9%)	44 F (57%)
Age (y)	67.84 ± 8.69	68.42 ± 11.16	66.1 ± 8.14
Age at onset (y)	61.64 ± 9.52	55.4 ± 18.1	–
Disease duration (y)	3.62 ± 2.49	14.98 ± 14.1	–
Familial history	0 Y (0%)	35 Y (50.73%)	–
MoCA score	26.56 ± 2.51	27.42 ± 2.61	27.21 ± 2.82
FTMTRS	–	19.41 ± 13.32	–
UPDRS part III	34.85 ± 12.71	–	–

PD, Parkinson's disease; ET, essential tremor; HC, healthy controls; F, females; M, males; Y, yes; MoCA, Montreal cognitive assessment; FTMTRS, Fahn-TolosaMarin Tremor Rating Scale; Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Data are indicated as mean ± standard deviation (SD). Percentages are indicated in brackets

Table. 2 Finger tapping kinematics

	PD (n= 44)	**ET (n= 69)**	**HCs (n= 77)**	p*	p**	p***
N MOV	50 (19.75)	38.13 (18.5)	50.91 (19.6)	<0.001	1	<0.001
CV ($Rhythm^K$)	0.12 (0.03)	0.1 (0.043)	0.08 (0.06)	0.005	<0.001	0.48
MOVEMENT AMPLITUDE	39.21 (20.81)	45.59 (18.34)	49.24 (12.98)	0.064	<0.001	0.053
MOVEMENT VELOCITY (Vel^K)	766.618 (410.57)	925.634 (308.39)	1053.36 (155.32)	0.005	<0.001	<0.001
AMPLITUDE SLOPE (Seq_Eff^K)	-0.18 (0.25)	-0.1 (-0.27)	-0.11 (0.16)	<0.001	0.003	0.43
VELOCITY SLOPE	-4.33 (-5.02)	-4.56 (-5.67)	-4.94 (-4.83)	1	1	1
CV ($Rhythm^K$)	0.12 (0.03)	0.1 (0.043)	0.08 (0.06)	0.005	<0.001	0.48
MOVEMENT AMPLITUDE	39.21 (20.81)	45.59 (18.34)	49.24 (12.98)	0.064	<0.001	0.053

PD, Parkinson's disease; ET, essential tremor; HC, healthy controls; N MOV, number of movements; CV, coefficient of variation (RhythmK). Movement amplitude is expressed in degrees; movement velocity (VelK) is expressed in degrees/sec. Amplitude slope is (Seq EffK) expressed in degrees/n mov. Velocity slope is expressed in (degrees/sec)/n mov. Data are indicated as median (interquartile range). **p* values from posthoc comparisons between PD and ET; ***p* values from post-hoc comparisons between PD and HC; ****p* values from post-hoc comparisons between ET and HC. Significant values are indicated in bold.

Table 3: Clinical and kinematic data of finger-tapping in patients with Parkinson's disease (PD), tested with and without their usual dopaminergic therapy (ON and OFF medication state), and healthy controls (HCs).

	HCs (n=158)	PD OFF (n=192)	PD ON (n=129)	p*	p**
Clinical data					
Sex	56 F	53 F	34 F	0.13	-
Age	66.02±12.6	66.8±9.16	66.2±9.10	0.88	-
MoCA	26.61±4.74	25.59±3.01	27.30±3.14	0.07	-
BDI	5.75±4.97	7.01±5.58	7.14±5.84	**0.04**	-
Disease duration	-	5.27±6.2	4.53±3.6	-	-
Most affected body side	-	100 R	69 R	-	-
MDS-UPDRS III	-	29.31±12.7	24.45 ± 12.36	-	**<0.001**
LEDD	-	399.64±272.35	407.67±289.32	-	-
Kinematic data					
N° mov	46.26 (16.41)	48.65 (13.89)	46.94 (15.13)	0.15	0.88
CV	0.09 (0.03)	0.14 (0.07)	0.14 (0.07)	**<0.001**	0.40
Movement velocity	1080.80 (252.8)	775.13 (283.26)	874.11 (288.26)	**<0.001**	**<0.001**
Movement amplitude	49.93 (13.48)	40.41 (13.11)	44.01 (12.41)	**<0.001**	**0.001**
Velocity slope	-6.39 (4.73)	-5.48 (4.28)	-5.68 (5.16)	0.06	0.87
Amplitude slope	-0.13 (0.21)	-0.26 (0.31)	-0.27 (0.27)	**<0.001**	0.91

The number of participants are in square brackets. Age and disease duration are expressed in years. MoCA: Montreal Cognitive Assessment, BDI: Beck Depression Inventory, R: right, MDS-UPDRS Part III: Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale, part III, LEDD: levodopa equivalent daily dose. N° MOV: number of movements, CV: coefficient of variation. Movement velocity is expressed in degrees/sec, movement amplitude in degrees. Velocity and amplitude slopes are expressed in (degree/sec)/n mov and (degree/n mov), respectively. Data are shown as mean values ± 1 standard deviation (SD). P values*: PD OFF condition vs HCs. P values**: PD OFF vs ON medication state. Significant values are shown in bold.

Table 4: Cluster analysis.

	Cluster 1 (n= 98)					Cluster 2 (n= 252)				
	CV									
	Min	Q1	Me	Q3	Max	Min	Q1	Me	Q3	Max
HCs	0.058	0.092	0.140	0.179	0.250	0.035	0.066	0.086	0.105	0.169
PD	0.059	0.170	0.200	0.242	0.390	0.040	0.080	0.100	0.120	0.170
	MOVEMENT VELOCITY									
	Min	Q1	Me	Q3	Max	Min	Q1	Me	Q3	Max
HCs	476.0	813.6	967.1	1100.8	1327.2	257.6	974.3	1108.2	1282.6	1693.1
PD	87.2	526.8	660.7	829.1	1418.1	50.4	692.9	823.6	1012.9	1580.6
	MOVEMENT AMPLITUDE									
	Min	Q1	Me	Q3	Max	Min	Q1	Me	Q3	Max
HCs	39.156	46.858	53.344	61.324	83.858	8.169	40.835	49.667	57.399	78.551
PD	11.430	32.912	41.400	52.320	67.361	4.170	32.348	41.315	47.967	78.100
	AMPLITUDE SLOPE									
	Min	Q1	Me	Q3	Max	Min	Q1	Me	Q3	Max
HCs	-1.145	-0.276	0.102	0.168	0.473	-0.588	-0.250	-0.148	-0.025	0.276
PD	-2.510	-0.557	-0.385	-0.138	0.340	-0.540	-0.230	-0.160	-0.050	0.210

Unsupervised clustering was performed using the mclust package in R (version 4.4.2), which applies Gaussian Mixture Models (GMM) for model-based clustering. The optimal number of clusters was selected using the Bayesian Information Criterion (BIC). We identified two clusters as the optimal solution. Cluster 1 was predominantly composed of Parkinson's disease patients (PD), with 80 out of 98 members belonging to this group. In contrast, Cluster 2 displayed a more balanced distribution, comprising 140 healthy controls (HCs) and 112 PD. The total number of subjects is indicated in square brackets. Min: Minimum value, Q1: first quartile — the value below which 25% of the data fall (also called the 25th percentile). Me: Median, Q3: third quartile, Max: Maximum value. CV: coefficient of variation. Movement velocity is expressed in degrees/sec, movement amplitude in degrees, amplitude slopes in (degree/n mov).

Table 5: Kinematic cut-off values obtained from the receiver operating characteristics (ROC) curves analysis.

	Cut-off values	AUC	p	Sensitivity	Specificity
N° MOV	46.17	0.54	0.15	0.52	0.6
CV	0.11	0.71	<0.001	0.63	0.7
MOVEMENT VELOCITY	952.33	0.80	<0.001	0.77	0.73
MOVEMENT AMPLITUDE	46.69	0.70	<0.001	0.68	0.61
VELOCITY SLOPE	-6.92	0.59	0.02	0.68	0.51
AMPLITUDE SLOPE	-0.17	0.62	<0.001	0.56	0.60

N° MOV: number of movements, CV: coefficient of variation, AUC: area under the curve. Movement velocity is expressed in degrees/sec, movement amplitude in degrees, velocity slope in (degree/sec)/n mov, amplitude slopes in (degree/n mov).

Table 6: Bradykinesia features in patients with Parkinson's disease (PD) and healthy controls (HCs).

		HCs [158]	PD OFF [192]
Normal movement	-	30 (19)	6 (3.1)
1 movement abnormality [HCs: 68 (43), PD OFF: 19 (9.9)]	D	8 (5.1)	3 (1.6)
	B	2 (1.3)	1 (0.5)
	H	21 (13.3)	4 (2.1)
	SE	37 (23.4)	11 (5.7)
2 movement abnormalities [HCs: 44 (27.8), PD OFF: 56 (29.2)]	D+B	2 (1.3)	3 (1.6)
	D+H	6 (3.8)	1 (0.5)
	D+SE	10 (6.3)	14 (7.3)
	B+H	16 (10.1)	25 (13)
	B+SE	7 (4.4)	10 (5.2)
	H+SE	3 (1.9)	3 (1.6)
3 movement abnormalities [HCs: 14 (8.9), PD OFF: 76 (39.6)]	D+B+H	8 (5.1)	40 (20.8)
	D+B+SE	1 (0.6)	14 (7.3)
	D+H+SE	1 (0.6)	2 (1.0)
	B+H+SE	4 (2.5)	20 (10.4)
4 movement abnormalities	D+B+H+SE	2 (1.3)	35 (18.2)

D: dysrhythmia, B: bradykinesia (movement slowness), H: hypokinesia (low amplitude movement), SE: sequence effect (amplitude slope). The total number of subjects included in the two groups is indicated in square brackets. Percentages are in round brackets.

Table 7: Bradykinesia features in patients with Parkinson's disease (PD) patients tested after an overnight withdrawal (OFF medication state) and with their usual dopaminergic therapy (ON medication state).

		PD OFF [129]	PD ON [129]
Normal movement	-	5 (3.9)	5 (3.9)
1 movement abnormality [PD OFF: 13 (10.1); PD ON: 19 (14.7)]	D	2 (1.6)	2 (1.6)
	B	1 (0.8)	1 (0.8)
	H	4 (3.1)	6 (4.7)
	SE	6 (4.7)	10 (7.8)
2 movement abnormalities [PD OFF: 34 (26.4); PD ON: 53 (41.1)]	D+B	1 (0.8)	3 (2.3)
	D+H	0 (0)	3 (2.3)
	D+SE	8 (6.2)	19 (14.7)
	B+H	15 (11.6)	19 (14.7)
	B+SE	7 (5.4)	4 (3.1)
	H+SE	3 (2.3)	5 (3.9)
3 movement abnormalities [PD OFF: 50 (38.8); PD ON: 39 (30.2)]	D+B+H	23 (17.8)	17 (13.2)
	D+B+SE	10 (7.8)	10 (7.8)
	D+H+SE	2 (1.6)	4 (3.1)
	B+H+SE	15 (11.6)	9 (7.0)
4 movement abnormalities	D+B+H+SE	27 (20.9)	12 (9.3)

D: dysrhythmia, B: bradykinesia (movement slowness), H: hypokinesia (low amplitude movement), SE: sequence effect (amplitude slope). The total number of subjects is indicated in square brackets. Percentages are in round brackets.

Table 8: Conditional probabilities of a participant belonging to either Parkinson's disease (PD) and healthy controls (HCs) groups based on specific bradykinesia features, their combinations and number of features (feat count).

		P(HCs|Feat Combination)	P(PD|Feat Combination)
Normal movement	-	83.3	16.7
1 movement abnormality [P(HCs|Feat Count)=78.2; P(PD|Feat Count)=21.8]	D	72.7	27.2
	B	66.7	33.3
	H	84	16
	SE	77.1	22.9
2 movement abnormalities [P(HCs|Feat Count)=44; P(PD|Feat Count)=56]	D+B	40	60
	D+H	85.7	14.3
	D+SE	41.7	58.3
	B+H	39	60.1
	B+SE	21.9	78.1
	H+SE	50	50
3 movement abnormalities [P(HCs|Feat Count)=15.5; P(PD|Feat Count)=84.4]	D+B+H	16.7	83.3
	D+B+SE	6.7	93.3
	D+H+SE	33.3	66.7
	B+H+SE	16.7	83.3
4 movement abnormalities	D+B+H+SE	5.4	94.6

D: dysrhythmia, B: bradykinesia (movement slowness), H: hypokinesia (low amplitude movement), SE: sequence effect (amplitude slope).

Table 9: Conditional probabilities of a Parkinson's disease (PD) participant belonging to either the OFF and ON medication state based on specific bradykinesia features, their combinations and number of features (feat count).

		P(PD OFF|Feat Combination)	P(PD ON|Feat Combination)
Normal movement (p=1)	-	50.0	50.0
1 movement abnormality [P(OFF|Feat Count)=40.6; P(ON|Feat Count)=59.4]	D	50.0	50.0
	B	50.0	50.0
	H	40.0	60.0
	SE	37.5	62.5
2 movement abnormalities [P(OFF|Feat Count)=39.1; P(ON|Feat Count)=60.9]	D+B	25	75
	D+H	0.0	100.0
	D+SE	29.6	70.4
	B+H	44.1	55.9
	B+SE	63.6	36.4
	H+SE	37.5	62.5
3 movement abnormalities [P(OFF|Feat Count)=56.3; P(ON|Feat Count)=43.8]	D+B+H	57.5	42.5
	D+B+SE	50.0	50.0
	D+H+SE	33.3	66.7
	B+H+SE	62.5	37.5
4 movement abnormalities	D+B+H+SE	69.2	30.8

D: dysrhythmia, B: bradykinesia (movement slowness), H: hypokinesia (low amplitude movement), SE: sequence effect (amplitude slope).

Table 10: Bradykinesia features in participants belonging to Cluster 2.

		HCs [140]	PD OFF [112]	P(HCs|Feat Comb)	P(PD|Feat Comb)
Normal movement	-	28 (20)	6 (5.4)	*82.3*	*17.6*
1 movement abnormality [HCs: 61 (43.6), PD OFF: 17 (15.2); *P(HCs/Feat Count)=78.2; P(PD/Feat*	D	4 (2.9)	2 (1.68)	*66.7*	*33.3*
	B	0 (0.0)	0 (0.0)	-	-
	H	21 (15.0)	4 (3.6)	*84.0*	*16.0*
	SE	36 (25.7)	11 (9.8)	*76.6*	*23.4*
2 movement abnormalities [HCs: 38 (27.1), PD OFF: 41 (36.6); *P(HCs/Feat Count)=48.1; P(PD/Feat Count)=51.9*	D+B	1 (0.7)	1 (0.9)	*50.0*	*50.0*
	D+H	6 (4.3)	1 (0.9)	*85.7*	*14.3*
	D+SE	7 (5.0)	6 (5.4)	*53.8*	*46.1*
	B+H	15 (10.7)	25 (22.3)	*37.5*	*62.5*
	B+SE	6 (4.3)	5 (4.5)	*60.0*	*40.0*
	H+SE	3 (2.1)	3 (2.7)	*50.0*	*50.0*
3 movement abnormalities [HCs: 12 (8.6), PD OFF: 42 (37.5); *P(HCs/Feat Count)=22.2; P(PD/Feat*	D+B+H	6 (4.3)	20 (17.9)	*23.1*	*76.9*
	D+B+SE	1 (0.7)	2 (1.8)	*33.3*	*66.7*
	D+H+SE	1 (0.7)	0 (0.0)	*100.0*	*0.0*
	B+H+SE	4 (2.9)	20 (17.9)	*16.7*	*83.3*
4 movement abnormalities	D+B+H+SE	1 (0.7)	6 (5.4)	*14.3*	*85.7*

PD. Parkinson's disease, HCs: healthy controls, D: dysrhythmia, B: bradykinesia (movement slowness), H: hypokinesia (low amplitude movement), SE: sequence effect. The total number of subjects included in the two groups are indicated in square brackets. Percentages are in round brackets. P from Mann-Whitney U test. Significant values are shown in bold. Numbers in italics indicate the conditional probabilities of a participant belonging to either PD and HCs groups based on specific bradykinesia features, their combinations (feat comb) and number of features (feat count). In Cluster 2, we noted a roughly equal representation from the PD and HCs. Compared to HCs, a higher number of patients showed abnormal movements ($p=0.005$ by Fisher's exact test). Finally, the number of bradykinesia features differed between PD and HCs included in Cluster 2 ($p<0.001$ by Mann-Whitney U test).

Table 11: Bradykinesia features in participants belonging to Cluster 1.

		HCs [18]	PD OFF [80]	P(HCs|Feat Comb)	P(PD|Feat Comb)
Normal movement	-	2 (11.1)	0 (0.0)	*100.0*	*0.0*
1 movement abnormality [HCs: 7 (38.9), PD OFF: 2 (2.5); *P(HCs/Feat Count)=77.3; P(PD/Feat*	D	4 (22.2)	1 (1.3)	*79.6*	*20.4*
	B	2 (11.1)	1 (1.3)	*66.1*	*33.9*
	H	0 (0.0)	0 (0.0)	-	-
	SE	1 (5.6)	0 (0.0)	*100.0*	*0.0*
2 movement abnormalities [HCs: 6 (33.3), PD OFF: 15 (18.8)**;** *P(HCs/Feat Count)=28.1; P(PD/Feat Count)=71.9*	D+B	1 (5.6)	2 (2.5)	*32.8*	*67.2*
	D+H	0 (0.0)	0 (0.0)	-	-
	D+SE	3 (16.7)	8 (10.0)	*26.8*	*73.2*
	B+H	1 (5.6)	0 (0.0)	*100.0*	*0.0*
	B+SE	1 (5.6)	5 (6.3)	*16.3*	*83.7*
	H+SE	0 (0.0)	0 (0.0)	-	-
3 movement abnormalities [HCs: 2 (11.1), PD OFF: 34 (42.5); *P(HCs/Feat Count)=5.4; P(PD/Feat*	D+B+H	2 (11.1)	20 (25.0)	*8.9*	*91.1*
	D+B+SE	0 (0.0)	12 (15.0)	*0.0*	*100.0*
	D+H+SE	0 (0.0)	2 (2.5)	*0.0*	*100.0*
	B+H+SE	0 (0.0)	0 (0.0)	-	-
4 movement abnormalities	D+B+H+SE	1 (5.6)	29 (36.3)	*3.3*	*96.7*

PD. Parkinson's disease, HCs: healthy controls, D: dysrhythmia, B: bradykinesia (movement slowness), H: hypokinesia (low amplitude movement), SE: sequence effect. The total number of subjects included in the two groups are indicated in square brackets. Percentages are in round brackets. Numbers in italics indicate the conditional probabilities of a participant belonging to either PD and HCs groups based on specific bradykinesia features, their combinations (feat comb) and number of features (feat count). Note that Cluster 1 included more PD patients than HCs. Compared to HCs, a higher number of patients showed abnormal movements ($p=0.02$ by Fisher's exact test). Finally, the number of bradykinesia features differed between PD and HCs included in Cluster 1 ($p<0.001$ by Mann-Whitney U test).

Table 12. Regression analysis conducted in the subsample of 129 Parkinson's disease (PD) patients tested in the ON and OFF medication state.

	standardized β	t	p
MDS-UPDRS III score	0.54	5.65	**<0.001**
LEDD	-0.30	-3.16	**0.002**
Sex	0.15	1.85	0.07
Age	-0.23	-2.68	**0.01**
MoCA	-0.19	-2.39	**0.02**

Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale, part III, LEDD: levodopa equivalent daily dose. MoCA: Montreal Cognitive Assessment. The analysis revealed a statistically significant model that explained 24.4% of the variance in the number of motor abnormalities [adjusted $R^2 = 0.244$, $F(5, 123) = 9.28$, $p<0.001$]. Other variables, including disease duration, Beck Depression Inventory (BDI) scores, and delta MDS-UPDRS III were excluded from the model as they did not significantly enhance its explanatory power.

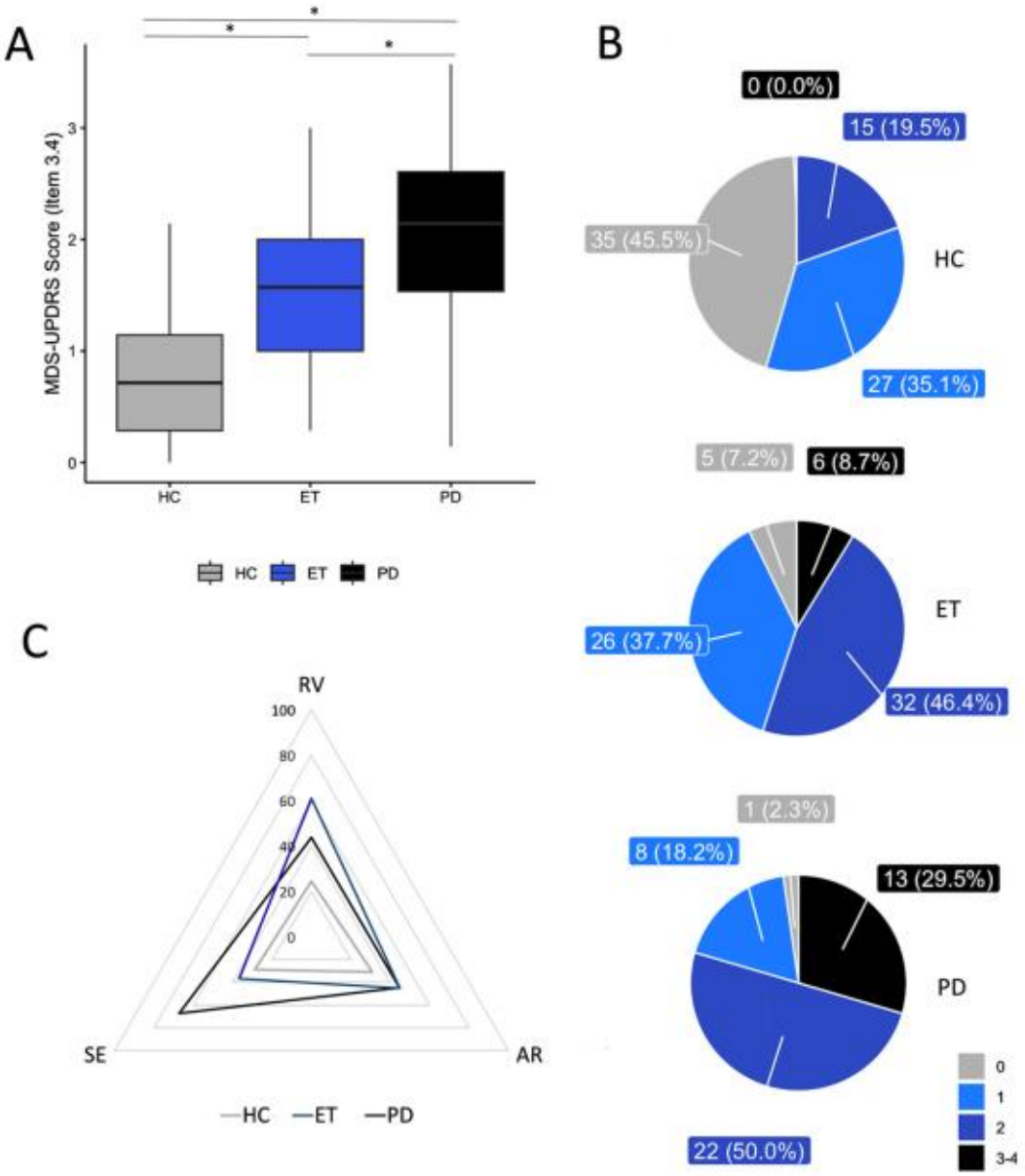
Table 13. Comparison between the kinematic parameters obtained with 2D and 3D reconstruction.

	2D	*3D*	*P value*
NMOV	53.06 ± 12.45	54.59 ±15.91	0.21
CV	0.22 ± 0.11	0.06 ± 0.017	0.00
AMP	63.57 ± 8.71	55.56 ± 6.57	0.00
AMPSL	-0.12 ± 0.17	-0.13 ± 0.16	0.75
VEL	1195.02 ± 394.61	111.22 ± 267.07	0.18
VELSL	-6.14 ± 4.78	-4.72 ± 4.71	0.25

NMOV= number of movements; CV= coefficient of variation; AMP= amplitude; AMPSL: slope of amplitude; VEL= velocity; VELSL= slope of velocity. Data are shown as mean ± standard deviation (SD). The p-value refers to the paired samples t-test.

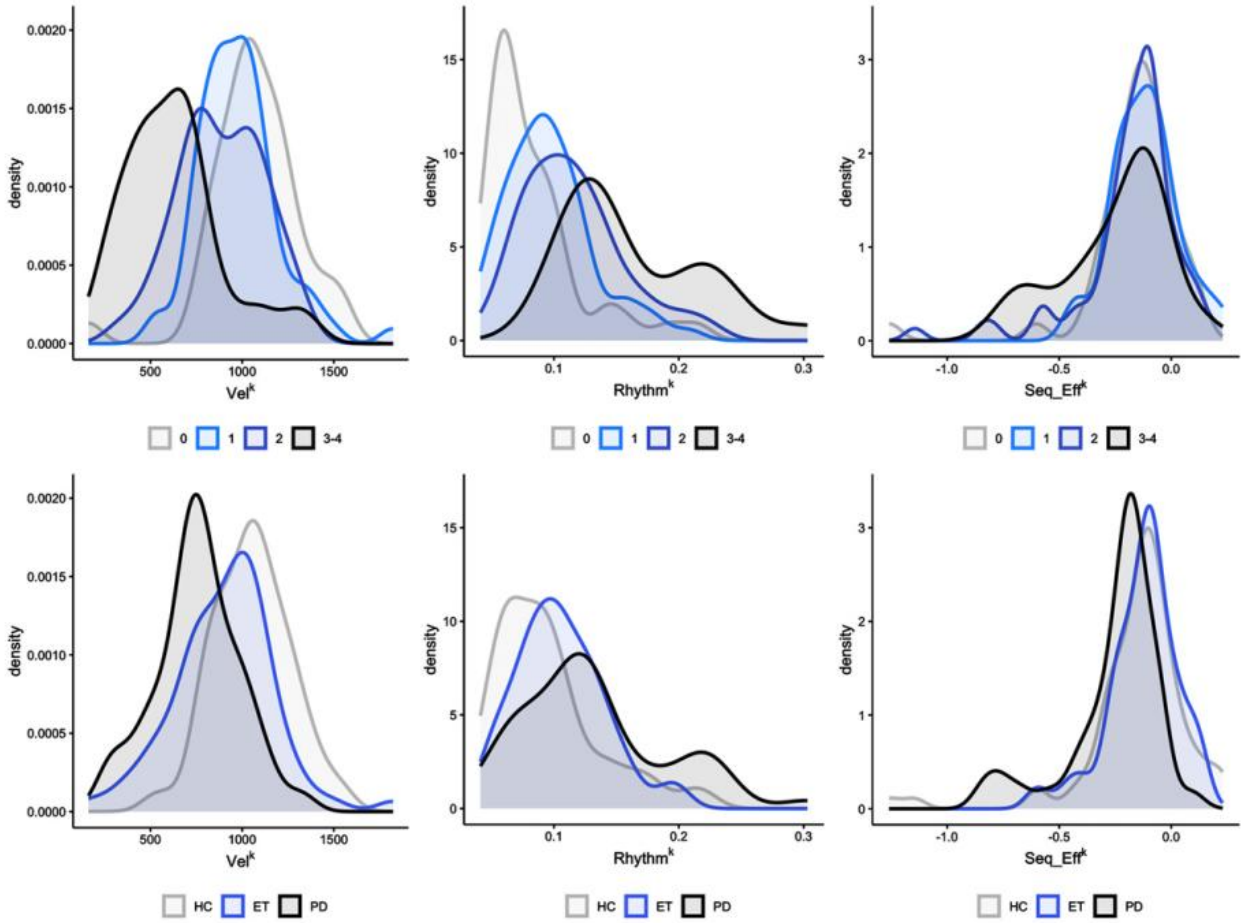
9. FIGURES

Figure 1. Blinded video evaluation results.



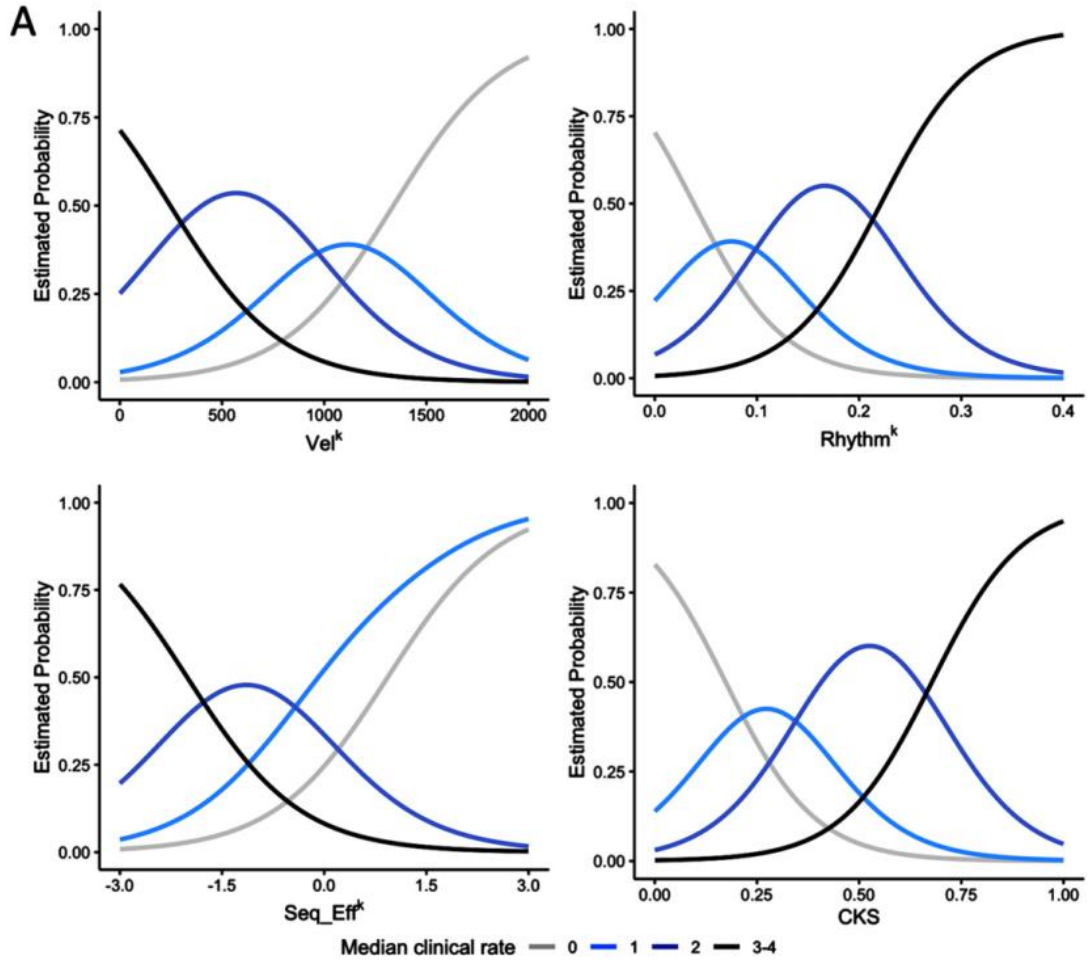
A) Finger tapping blinded video rating scores in healthy controls (HC), patients with Parkinson's disease (PD), and essential tremor (ET), according to the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Horizontal lines denote median values. Asterisks indicate $p < 0.05$ in the post hoc comparisons. B) Number of subjects (percentage are in brackets) within the HC, ET, and PD groups who obtained specific clinical scores (ranging from 0 to 4) at the blinded video evaluations. C) Percentage of subjects within the HC, ET, and PD groups showing specific movement abnormalities at the blinded video evaluation, including reduced velocity (RV), altered rhythm (AR), and sequence effect (SE) (PD group: RV vs. AR: $p = 0.58$; AR vs. SE: $p = 0.026$; RV vs. SE: $p = 0.026$; ET group: RV vs. AR: $p = 0.043$; AR vs. SE: $p = 0.19$; RV vs. SE: $p = 0.003$; HC group: RV vs. AR: $p = 0.23$; AR vs. SE: $p = 0.43$; RV vs. SE: $p = 0.42$). Note that movement slowness was the most prominent abnormality and it differed between PD and ET, being much lower in HC (RV: PD vs. ET: $p = 0.012$, PD vs. HC: $p = 0.002$; ET vs. HC: $p < 0.001$). Irregular movement rhythm differentiates controls from patients, but not PD from ET (AR: PD vs. ET: $p = 0.55$, PD vs. HC: $p = 0.03$; ET vs. HC: $p = 0.03$). The SE was more prevalent in PD than in ET and HC, but it did not differ between ET and HC (SE: PD vs. ET: $p < 0.001$, PD vs. HC: $p < 0.001$; ET vs. HC: $p = 0.15$).

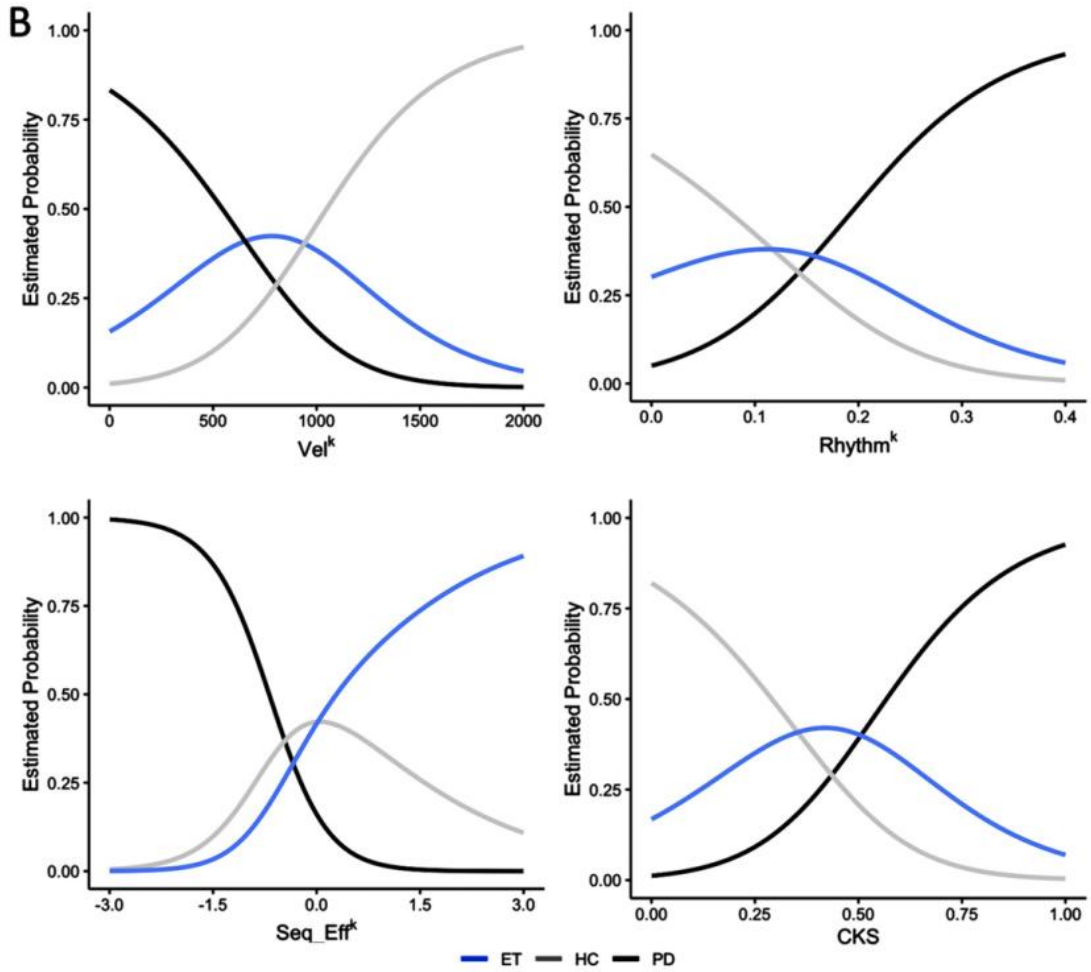
Figure 2. Stratified density plots.



Upper part: Density plots were used to evaluate the overlapping in the distribution of the kinematic data based on the median score (ranging from 0 to 4) given by the 7 raters. Note the marked overlapping between data curves, indicating that a given clinical score reflected a wide range of kinematic values in participants. Velocity is expressed as degrees/s (Vel^K). The coefficient of variation (CV), computed by the standard deviation/mean value of the inter-tap intervals, expresses movement rhythm (with higher CV values representing a lower regularity of repetitive movements) ($Rhythm^K$). Amplitude slope is expressed in (degrees/s)/n.mov ($Seq\ Eff^K$). Lower part: distribution of kinematic parameters among the three groups of participants (HC: healthy controls, ET: essential tremor, PD: Parkinson's disease). Note that the PD group had the lowest Vel^K values (left-hand graph). However, Vel^K greatly overlapped in ET and HC. The overlapping of kinematic data between the three groups was even greater for the $Rhythm^K$ and $Seq\ Eff^K$ (middle and right-hand graph).

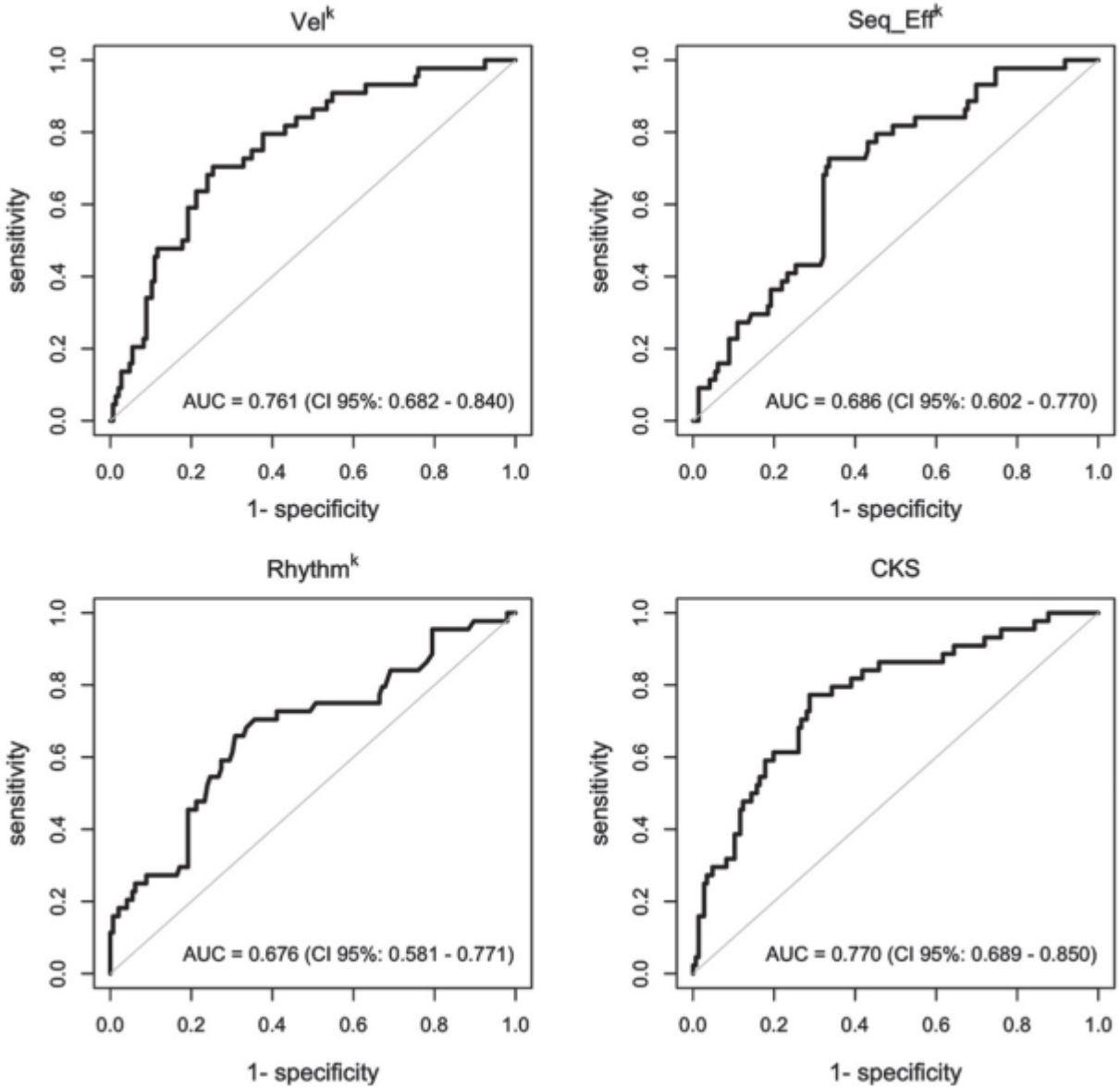
Figure 3. Ordinal and multinomial logistic regression analysis results.





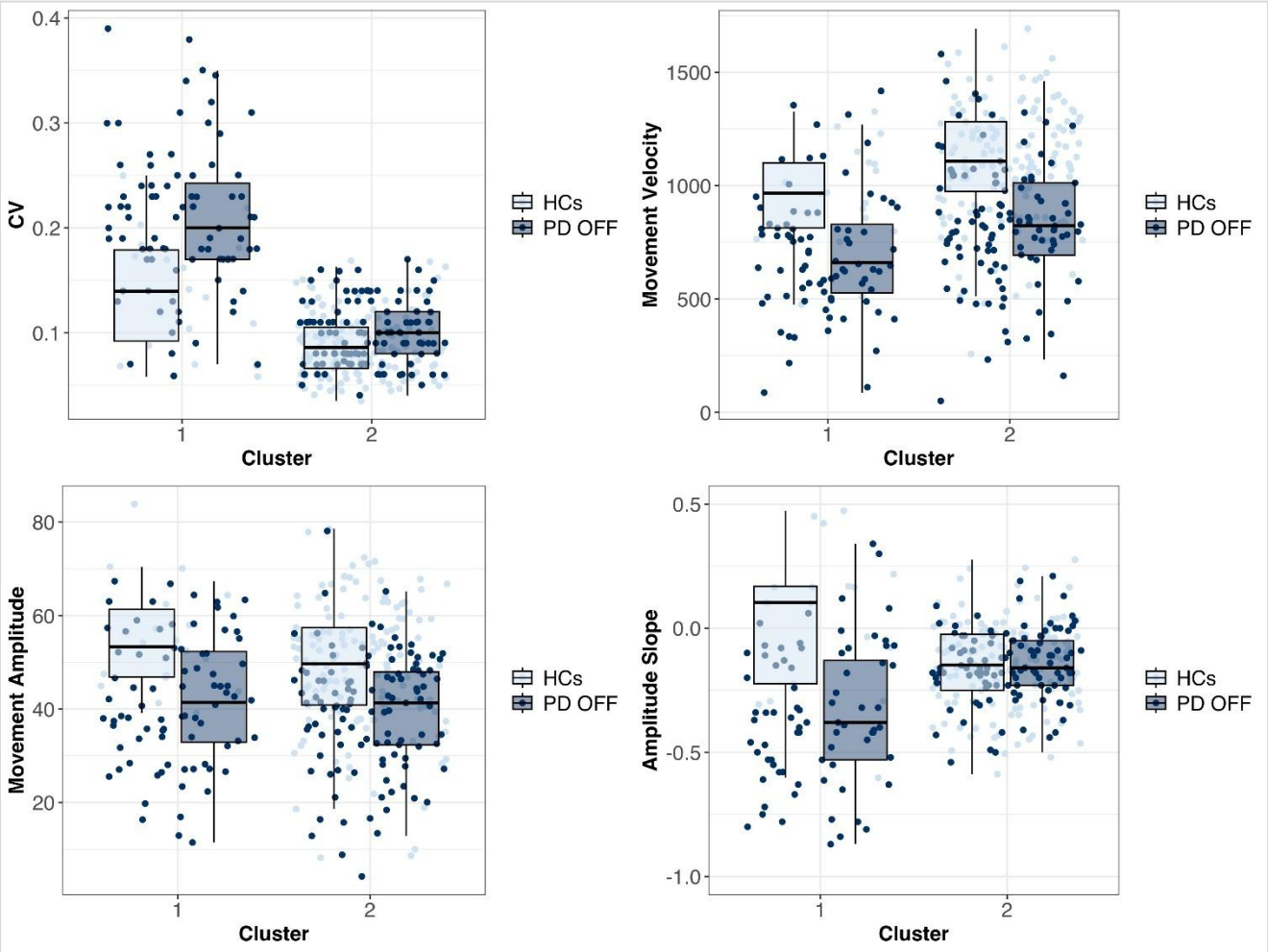
A) The figure depicts the probability of belonging to a specific clinical score category (0, 1, 2, or 3-4) based on individual kinematic parameters, i.e., movement velocity (VelK), coefficient of variation (RhythmK), and amplitude slope (Seq EffK), and on the combined kinematic score (CKS). Note that subjects with high CKS, i.e., greater than 0.6, had a high probability of being classified as bradykinetic, i.e., with Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) clinical scores higher than 2. The opposite occurred for subjects with low CKS score (<than 0.2), which had a high probability of being classified as normal (MDS-UPDRS clinical scores = 0). Intermediate CKS values, however, correspond to a low probability of being correctly classified as bradykinetic or not bradykinetic. B) The figure depicts the probability of belonging to a specific diagnostic group (HC, healthy controls; ET, essential tremor; PD, Parkinson's disease) based on individual kinematic parameters, and on the CKS. Note that subjects with CKS values greater than 0.7 had a high probability of belonging to the PD group, and a very low probability of belonging to the HC group. The opposite was observed for subjects with low CKS score values (lower than 0.2), which had a high probability of being normal subjects and a very low probability of belonging to the PD group. At intermediate CKS values corresponded comparable probabilities of belonging to the PD, ET, and HC groups

Figure 4. Receiver operating characteristic (ROC) curves.



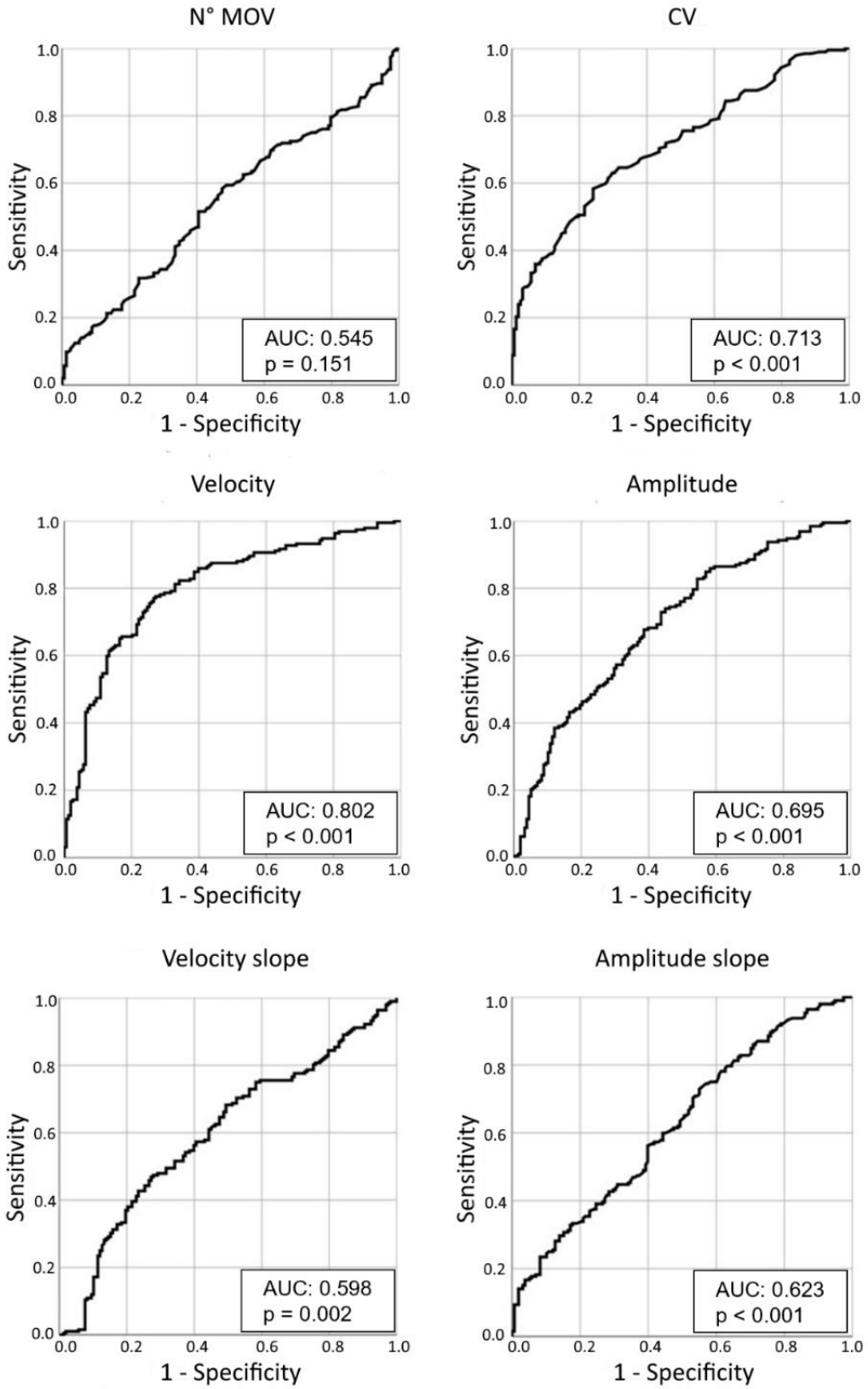
ROC curves were used to graphically represent and to determine the capacity of the kinematic variables and of the combined kinematic score (CKS) to evaluate the clinical score category and the diagnostic group in participants. The value of area under the ROC curve (AUC) was considered to measure for how well the model can discriminate between subjects

Figure 5: Cluster analysis results.



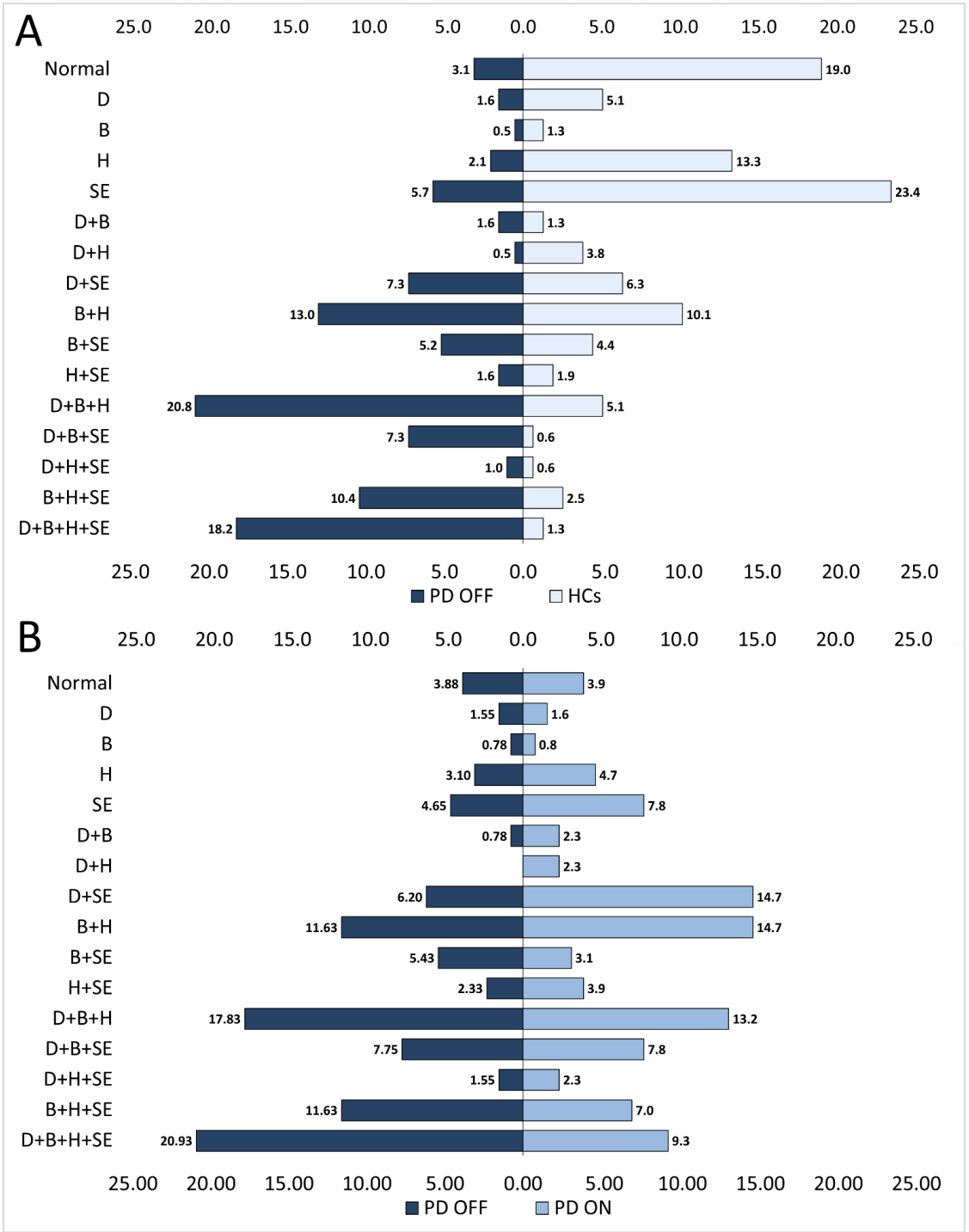
Unsupervised clustering was performed using the mclust package in R (version 4.4.2), which applies Gaussian Mixture Models (GMM) for model-based clustering. The optimal number of clusters was selected using the Bayesian Information Criterion (BIC). We identified two clusters as the optimal solution. Cluster 1 was predominantly composed of Parkinson's disease patients (PD), evaluated in their OFF-medication state, with 80 out of 98 members belonging to this group. In contrast, Cluster 2 displayed a more balanced distribution, comprising 140 health controls (HCs) and 112 PD. CV: coefficient of variation. Movement velocity is expressed in degrees/sec, movement amplitude in degrees, amplitude slopes in (degree/n mov).

Figure 6: Receiver operating characteristic (ROC) curves.



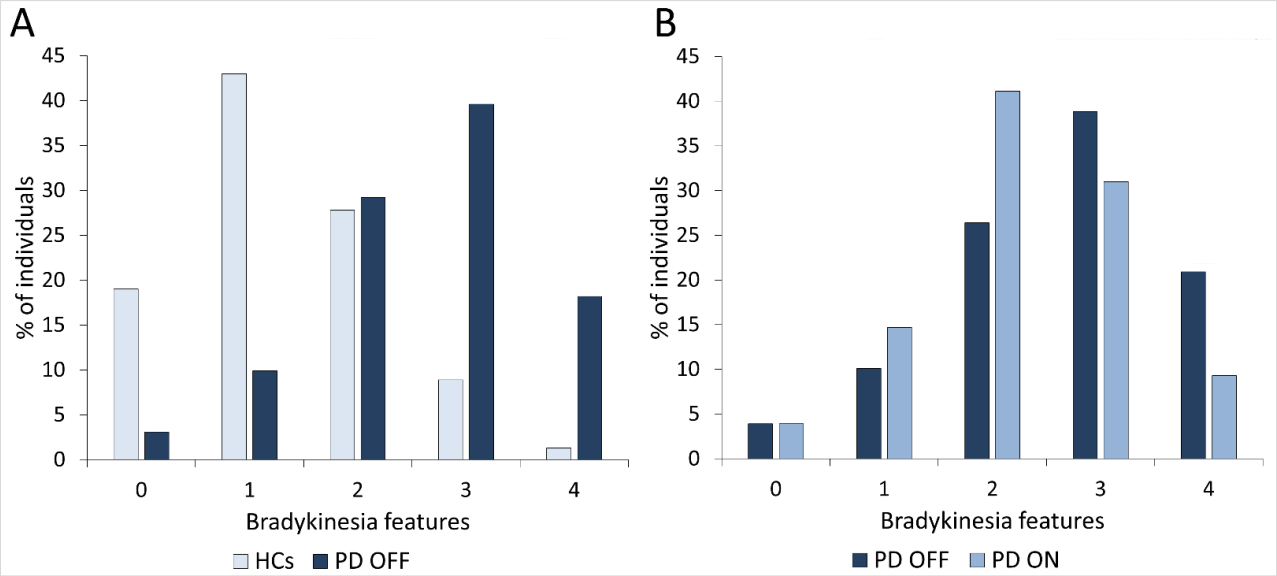
ROC curves were used to graphically represent the diagnostic properties of the finger-tapping kinematic variables (number of movements, i.e., N° MOV, coefficient of variation, i.e., CV, movement velocity and amplitude, velocity and amplitude slope, i.e., sequence effect). The value of area under the ROC curve (AUC) measures how well the model can discriminate between subjects.

Figure 7: Bradykinesia features and their combinations in patients with Parkinson's disease (PD) and healthy controls (HCs).



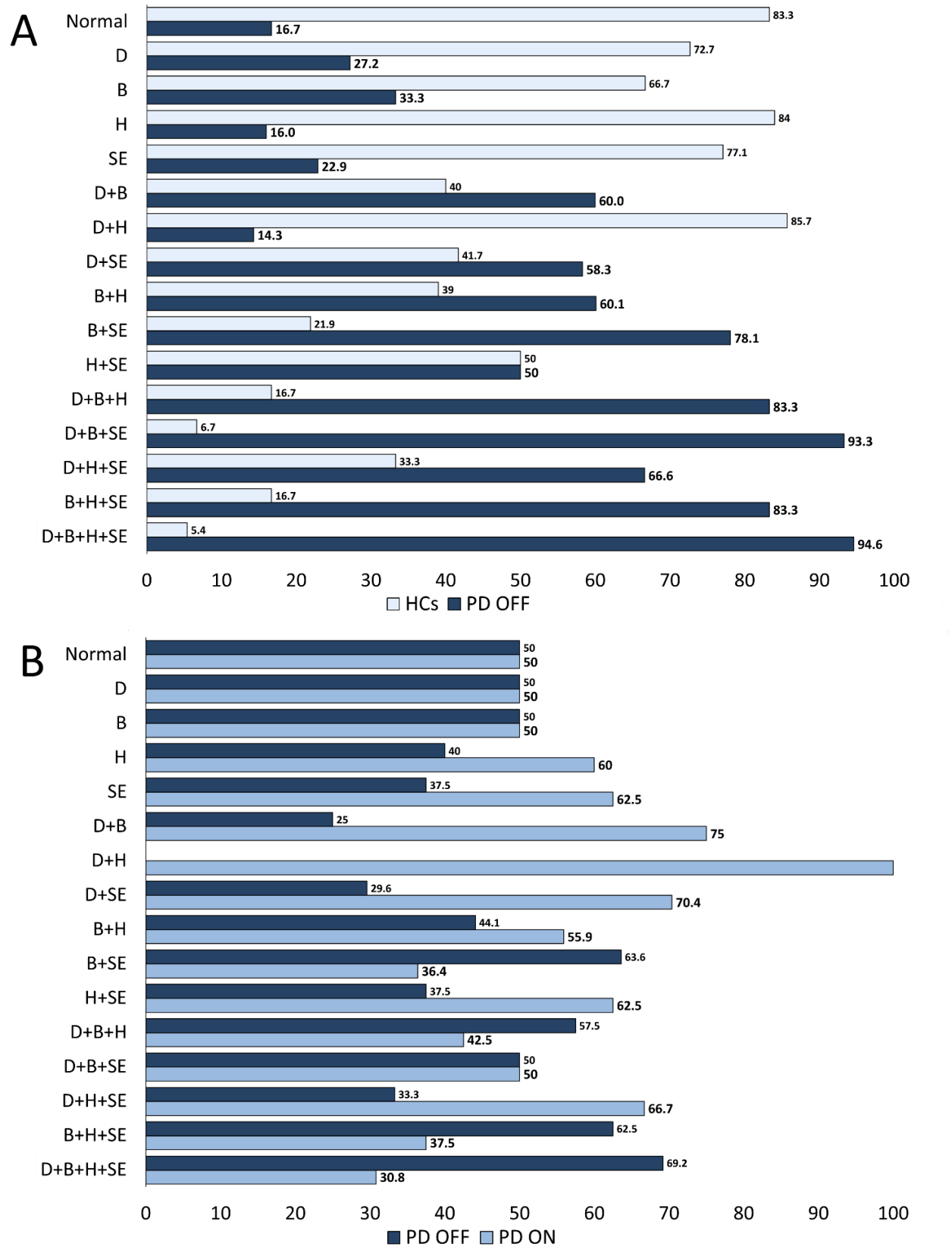
Numbers indicate percentages. The motor alterations were determined in each study participant based on the cut-offs from the analysis of the Receiver Operating Characteristic (ROC) curves. Panel A shows data of 192 PD patients, tested in the OFF state, that is without their usual dopaminergic therapy (left), and 158 HCs (right). Panel B shows data collected in a subsample of 129 PD patients tested with (ON, right) and without (OFF, left) their usual dopaminergic therapy. D: dysrhythmia, B: bradykinesia (movement slowness), H: hypokinesia (low amplitude movement), SE: sequence effect (amplitude slope).

Figure 8: Number of bradykinesia features in Parkinson's disease (PD) patients and elderly healthy controls (HCs).



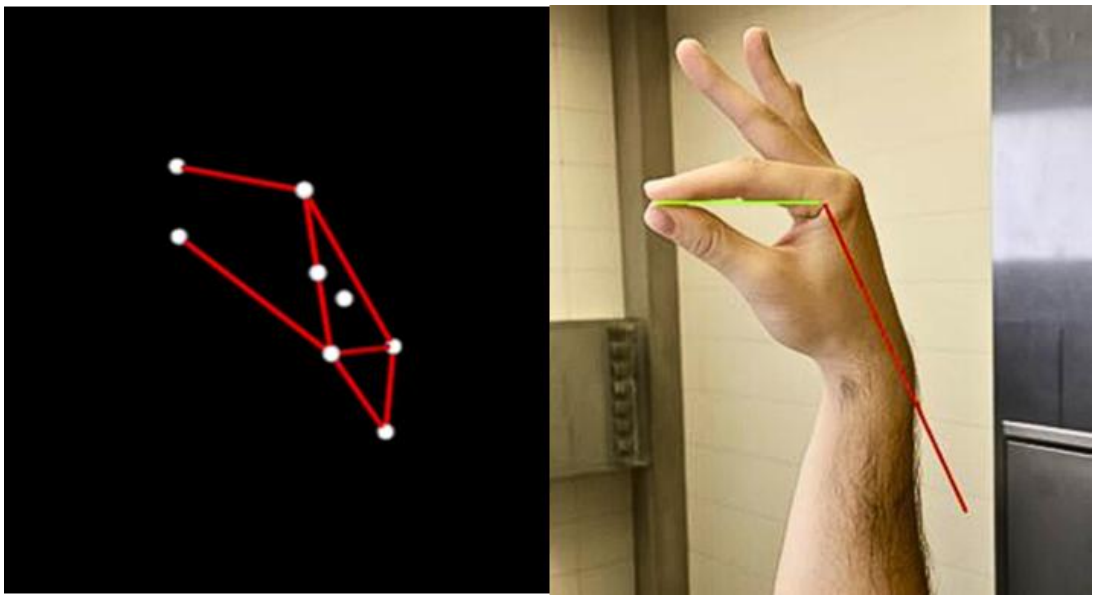
Part A shows data of 192 PD patients, tested without their usual dopaminergic therapy (OFF condition state) and 158 HCs, while part B shows data collected in a subsample of 129 PD patients tested with and without their usual dopaminergic therapy (ON and OFF condition state). Please note that the number of bradykinesia features differed between patients and controls ($p<0.001$ by Mann-Whitney U test), and that dopaminergic therapy impacted on the number of bradykinesia features in patients ($p<0.001$ by Wilcoxon signed-rank test).

Figure 9: Conditional probabilities.



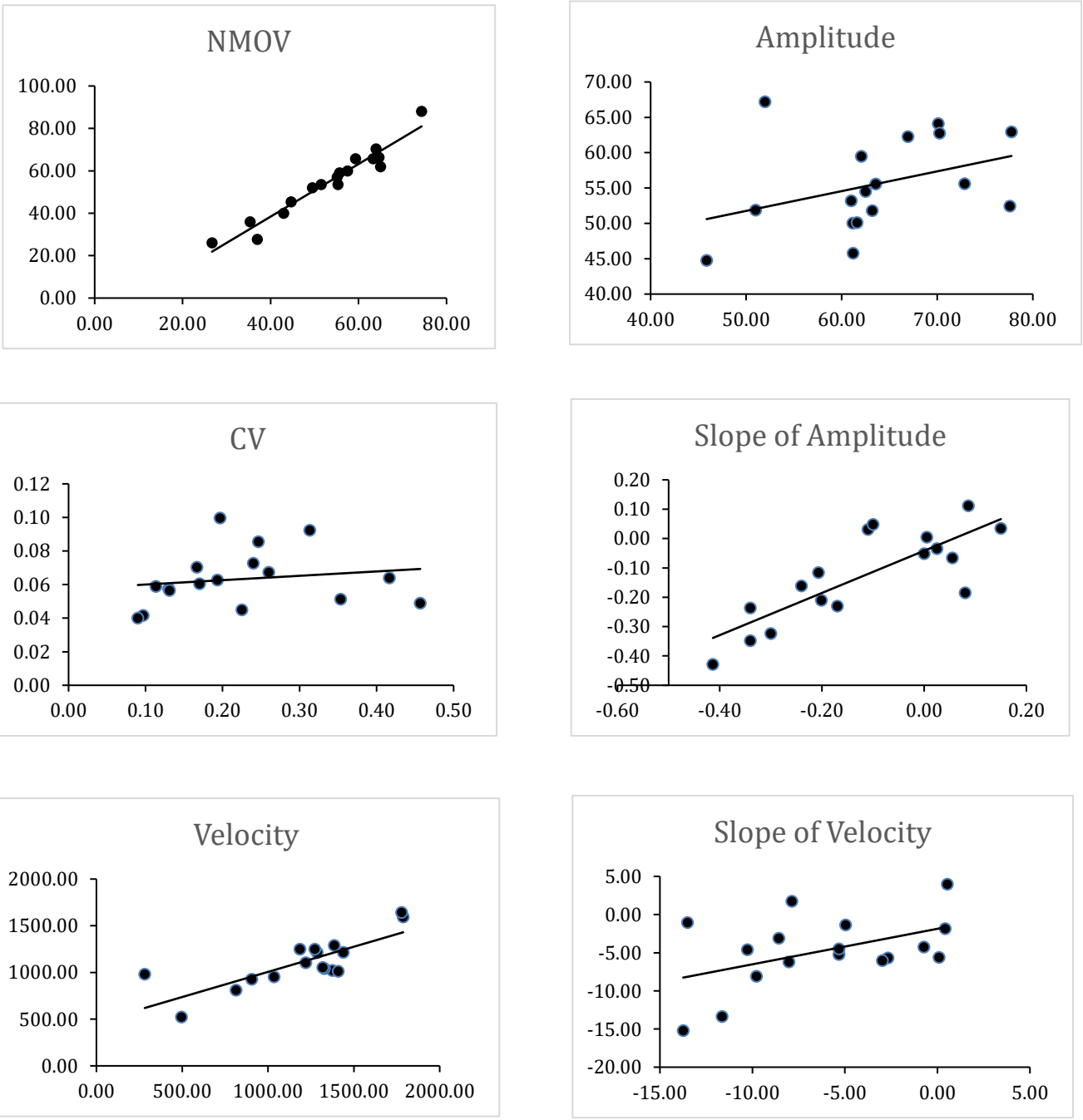
We calculated the conditional probabilities of a participant belonging to (A) either Parkinson's disease (PD) and healthy controls (HCs) groups or (B) OFF and ON medication state based on specific bradykinesia features and combinations.

Figure 10. Comparison of Finger Tapping Test Acquisition: Optoelectronic vs. Computer Vision Systems



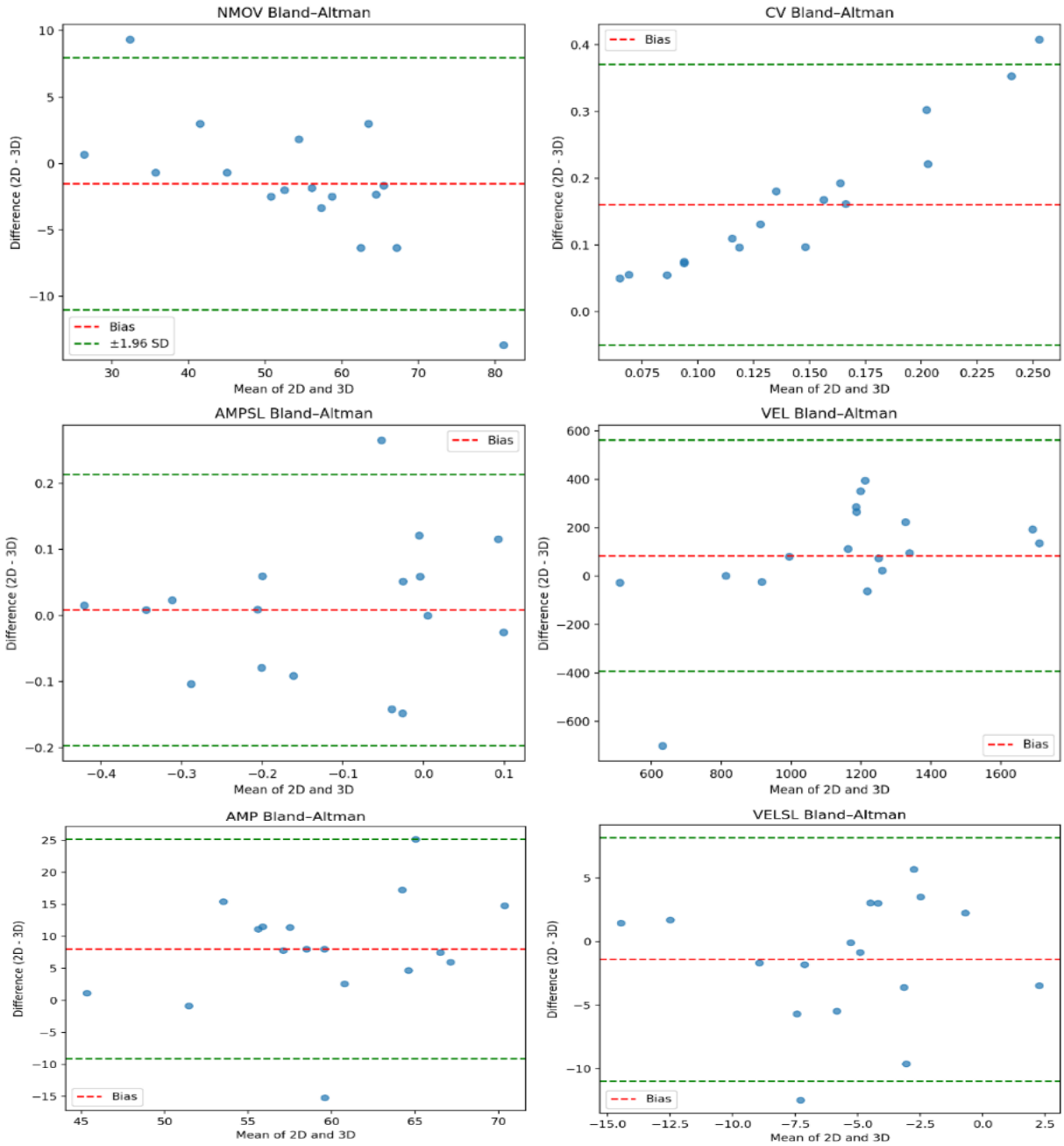
Example of kinematic recording of the Finger Tapping (FT) test using an optoelectronic system (left) and video frame of the same test processed with Computer Vision (CoV) techniques (right).

Figure 11. Correlations between the main 2D computer vision and 3D kinematic parameters.



NMOV = number of movements; CV = coefficient of variation;

Figure 12. Agreement analysis between 2D and 3D kinematic reconstructions, conducted using Bland–Altman plots.



NMOV= number of movements; CV= coefficient of variation; AMP= amplitude; AMPSL: slope of amplitude; VEL= velocity; VELSL= slope of velocity.