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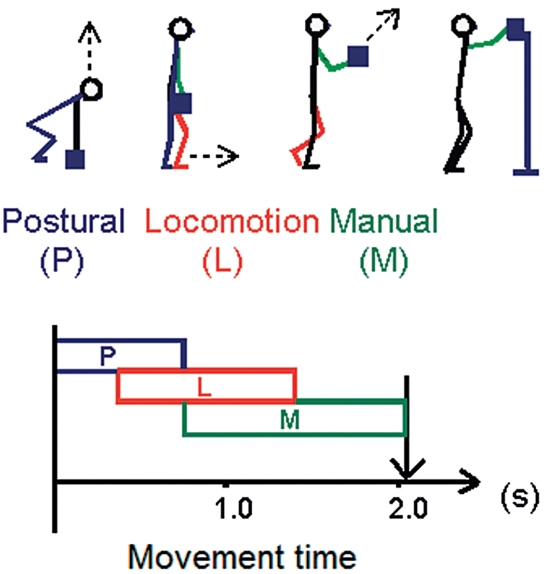
Parkinson's disease and motor function

– A validation of the PLM method



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- A Validation of the PLM Method

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Parkinson's Disease and Motor Function

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I have always believed that hope is that stubborn thing inside us that insists, despite all the evidence to the contrary, that something better awaits us so long as we have the courage to keep reaching, to keep working, to keep fighting. *President Barak Obama, November 7, 2012*

To Filippa and Theodore

There's nothing that can help you understand your beliefs more than trying to explain them to an inquisitive child.

Frank A. Clark

Parkinson's Disease and Motor Function

A Validation of the PLM Method

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ABSTRACT

Aim: To validate the Posturo-Locomotor-Manual (PLM) test, an objective movement measurement system designed to measure movement disability in patients with Parkinsonism.

Method: The reliability of the PLM test was determined in a test-retest procedure performed in 37 healthy controls (Study III). Correlations between the PLM test and clinical ratings with the Unified Parkinson's Disease Rating Scale motor section (UPDRS III) were investigated in 73 patients with Parkinsonism (47 with Parkinson's disease, 17 with multiple system atrophy, and 9 with progressive supranuclear palsy) who performed the PLM test and underwent UPDRS III rating in simultaneous assessments (Study II). The ability of the PLM test to discriminate between healthy controls and patients with Parkinsonism, between patients with Parkinson's disease and patients with atypical Parkinsonism, and between patients with multiple system atrophy and patients with progressive supranuclear palsy was evaluated in 132 patients (56 with Parkinson's disease, 53 with multiple system atrophy, and 23 with progressive supranuclear palsy) using multiple logistic regression analysis (Study III). To ensure that the accuracy of the original semiautomatic PLM method was maintained in a new automatic implementation, QbTestMotus, the old and new test methods were performed simultaneously in 61 patients and the correlation between the two techniques was analyzed (Study I). Finally, the PLM test was used in parallel with UPDRS III in a clinical pilot trial evaluating the effect of repetitive transcranial magnetic stimulation in 10 patients with early Parkinson's disease (Study IV).

Results: The PLM test had excellent test-retest reliability and discriminated effectively between healthy persons and patients with Parkinsonism (AUC 0.99). There was a fair to good correlation between the PLM test and UPDRS III in all measured variables except for the manual variable (M). The ability

of the PLM test to discriminate between PD patients and patients with atypical Parkinsonism was improved (to AUC=0.91) by combining two PLM variables. There was a good coherence between the original semiautomatic PLM test and the QbTestMotus. UPDRS III ratings indicated that repetitive transcranial magnetic stimulation over the motor cortex potentiated the medication effect in the 10 patients with early Parkinson's disease, but this effect was not detectable using the PLM test.

Conclusion: The automated implementation of the PLM test (QbTestMotus) generates data that are consistent with the measurements made with an older semi-automated method. The PLM test is a reliable and objective instrument for measuring motor function in ambulatory patients with Parkinsonism. It can distinguish between Parkinson's disease and atypical Parkinsonism in patients at intermediate to advanced stages of the disease, but cannot reliably detect acute treatment response in early-stage Parkinson's disease with symptoms predominantly from the upper limbs.

Keywords: PLM test, objective movement analysis, objective quantification, L-DOPA test

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SAMMANFATTNING PÅ SVENSKA

Parkinsons sjukdom och motorisk funktion

- En validering av PLM metoden

Syfte: Att validera den objektiva optoelektroniska mätmetoden Posturo-Locomotor-Manual (PLM) test, som utvecklats för att mäta rörelseoförmåga vid Parkinsons sjukdom.

Metod: PLM testets tillförlitlighet utvärderades genom upprepad testning av 37 friska kontrollpersoner i olika åldrar. Vi studerade hur väl PLM testet korrelerar med den kliniska skattningsskalan Unified Parkinson Disease Rating Scale III genom att genomföra parallella PLM tester och kliniska skattningar på 73 patienter med parkinsonism (47 av dessa med Parkinsons sjukdom (PS), 17 med multipel systematrofi (MSA) och 9 med progressive supranukleär pares PSP) före och efter en engångsdos L-DOPA. PLM testets förmåga att urskilja friska kontroller från patienter med parkinsonism undersöktes genom att analysera testresultat från 37 friska kontrollpersoner och 132 patienter (56 PS, 53 MSA och 23 PSP) med multipel logistisk regressionsanalys. En automatiserad version av PLM-testet QbTestMotus evaluerades parallellt med den tidigare semi-automatiska metoden för att verifiera bibehållen mätnogrannhet. I en liten klinisk pilotstudie på patienter med tidig PS användes PLM testet parallellt med UPDRS för att utvärdera den eventuella effekten av repetitiv transkraniell magnetstimulering på rörelsesymptom.

Resultat: PLM testet har en hög reliabilitet och kan effektivt skilja mellan friska personer och patienter med parkinsonism. Det finns en relativt god korrelation mellan PLM testet och UPDRS III och PLM testets diskriminerande förmåga avseende Parkinsons sjukdom och atypisk parkinsonism (MSA och PSP) var måttlig (AUC 0.82) men ökade till god då två PLM variabler kombinerades i diskriminationsanalysen (AUC 0.91). Automatiserade mätningar med QbTestMotus förändrar endast marginellt mätresultaten. PLM-testet lyckades inte på tidiga PS patienter mäta de förbättringar i rörelse-funktion efter magnetstimulering som registrerades med UPDRS III.

Slutsats: Den automatiserade implementeringen av PLM testet (QbTestMotus) genererar data som stämmer överens med tidigare metods mätningar. PLM testet är ett tillförlitligt och objektivt mätinstrument för att

mäta motorisk funktion hos ambulerande patienter med parkinsonism och kan skilja mellan Parkinsons sjukdom och atypisk parkinsonism hos patienter i intermediärt till avancerat skede av sjukdomsförloppet. PLM testet kan inte tillförlitligt detektera akuta behandlingssvar vid Parkinsons sjukdom i tidigt skede.

LIST OF PAPERS

This thesis is based on the following studies, which are referred to in the text by their Roman numerals.

I. **Zackrisson, T.**, Holmberg, B., Johnels, B., Thorlin, T. (2010). A new automated implementation of the Posturo-Locomotion-Manual (PLM) method for movement analysis in patients with Parkinson's disease. Acta Neurologica Scandinavica, 123:4, 274–279.

II. **Zackrisson, T.**, Bergquist, F., Holmberg, B., Johnels, B., Thorlin, T. (2013). Evaluation of the objective Posturo-Locomotor-Manual (PLM) method in patients with Parkinsonian syndromes. Frontiers in Neurology, 4:95.

III. **Zackrisson, T.**, Bergquist, F., Eklund, M., Holmberg, B., Thorlin, T. (2013). The discriminating properties of an optoelectronic movement analysis method in patients with Parkinsonism. Journal of Motor Behavior, *45:5, 415-422*

IV. *Revesz, D., ***Zackrisson, T.**, Hartelius, L., Eriksson, B., Holmberg, B., Thorlin, T. Effects of rTMS on motor symptoms in patients with early-stage Parkinson's disease.
* contributed equally
Manuscript submitted

CONTENT

ABBREVIATIONS

ANOVA	Analysis of variance
AUC	Area Under the Curve
H&Y	Hoehn and Yahr
ICC	Intraclass correlation coefficient
L phase	Locomotor phase of the PLM method
L-DOPA	(L-3,4-dihydroxyphenylalanine)
LED	L-DOPA equivalent dose
M phase	Manual phase of the PLM method
MDS-UPDRS	Movement Disorder Society Unified Parkinson's Disease Rating Scale
MSA	Multiple system atrophy
MT	Movement time
MT_1, MT_2	First and second movement time (healthy controls)
NINDS-SPSP	National Institute of Neurological Disorder and Stroke and the Society of PSP
OFF	Unmedicated state
ON	Medicated state
P phase	Postural phase of the PLM method
PD	Parkinson's disease
PLM test	Posturo-Locomotor-Manual test
PSP	Progressive supranuclear palsy

ROC	Receiver-operating characteristic
rTMS	Repetitive transcranial magnetic stimulation
SD	Standard deviation
SEM	Standard error of the mean
SI	Simultaneity index
UK PDSBB	United Kingdom Parkinson's Disease Society Brain Bank
UPDRS	Unified Parkinson's Disease Rating Scale
UPDRS III	Unified Parkinson's Disease Rating Scale, motor section

DEFINITIONS IN BRIEF

Atypical Parkinsonism	Movement disorders with similar symptoms to Parkinson's disease, but caused by a more widespread neuronal degeneration. Those discussed in this thesis are multiple system atrophy (MSA) and progressive supranuclear palsy (PSP).
Bradykinesia	Decreased amplitude and frequency in repeated movements, as well as a slowness in movement.
Parkinsonism	Charachterized by a combination of bradykinesia, resting tremor, rigidity, and postural instability.
Parkinson's disease	A degenerative movement disorder caused by loss of dopamine-containing neurons in the central nervous system and characterized by Parkinsonism.
Rigidity	Resistance to passive movements.

1 INTRODUCTION

1.1 History

In 1817, when James Parkinson described the condition that we now know as Parkinson's disease (PD) in "An Essay on the Shaking Palsy", he had made no use of particular tools or rating scales. Some fifty years later, however, Jean-Martin Charcot, a neurologist at the Salpêtrière Hospital in Paris, used hand dynamometers to show that the "shaking palsy" was not a palsy at all. Charcot therefore rejected the early term "paralysis agitans" in favor of the term "Parkinson's disease" [1]. In this way, an objective measurement device contributed to a redefinition of the syndrome of Parkinsonism as early as the 19th century.

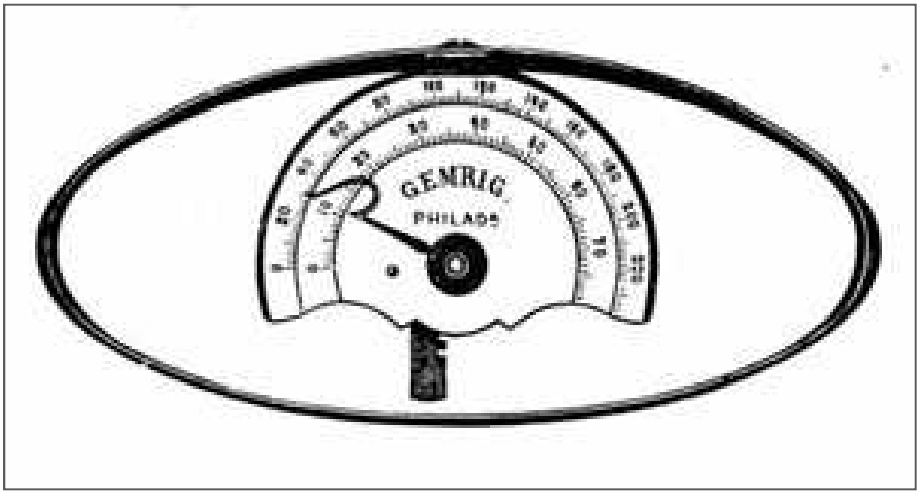

Figure 1. Dynamometer.

Historically, methods to objectively measure and characterize movements have had an important place in the development of neurology as a specialty. In the 1800s, the sphygmograph (initially developed for radial artery pulse recordings) provided information that helped differentiate the movement disturbances observed in PD from those seen in multiple sclerosis [1-3].

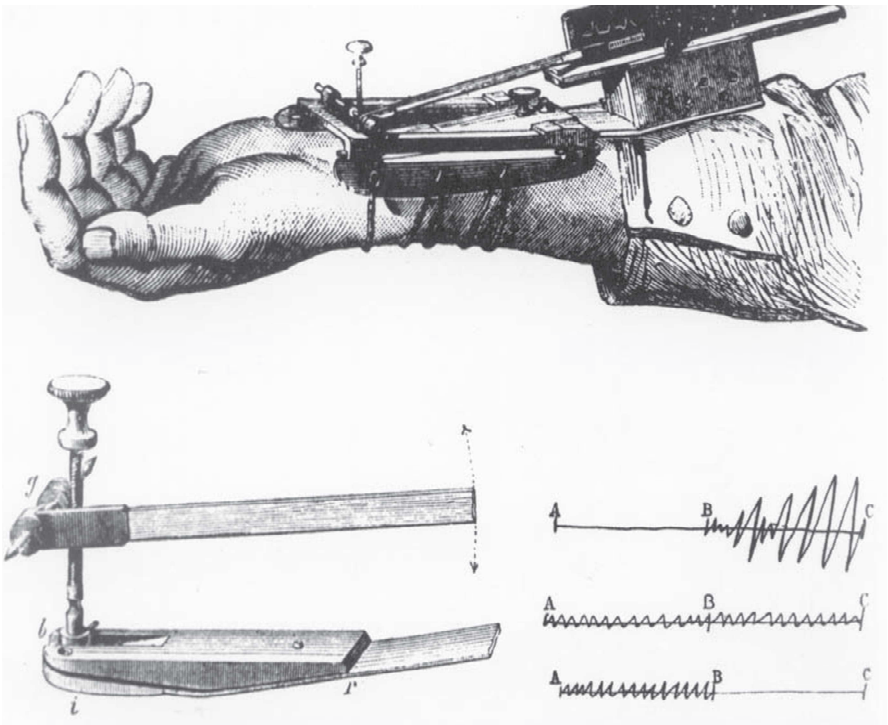

Figure 2. The sphygmograph (from Dictionnaire Encyclopédique des Sciences Médicales, Ser. 3, Vol. 11, pp. 208–209, 1883). Drawings from Charcot's lesson on tremor classification. AB indicates rest and BC represents action. Top: multiple sclerosis; middle and bottom: PD.

Early characterizations of gait disturbances were made with simple footprint techniques, for example in George Gilles de la Tourette's doctoral thesis "Etudes Cliniques et Physiologiques sur la Marche" ("Clinical and Physiological Studies on the Gait"). This method made it possible to record differences in gait characteristic of PD, Friedreich's ataxia, and neurosyphilis [4].

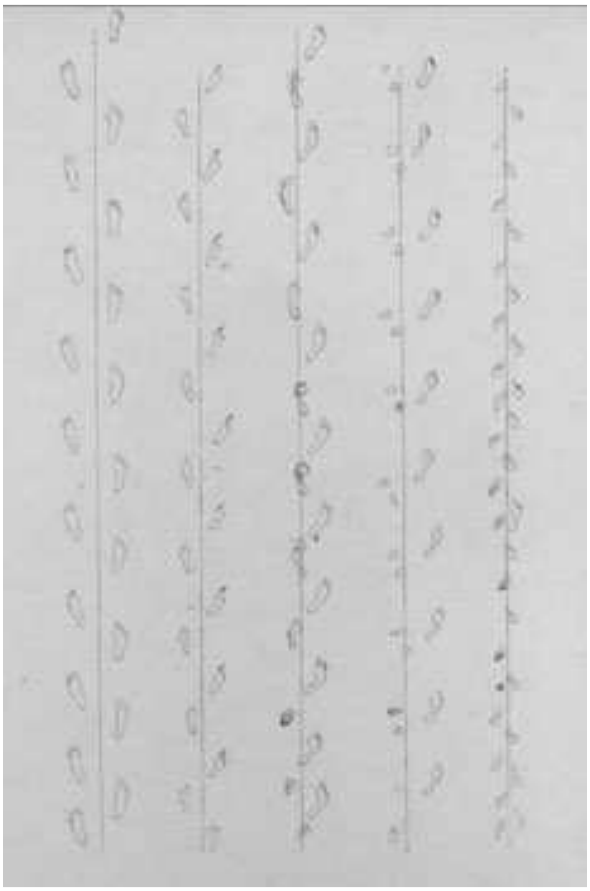

Figure 3. Footprint diagrams from the doctoral thesis of Gilles de la Tourette (1886). This student work analyzed and illustrated the footprints of ataxic patients with conditions such as PD, locomotor ataxia (neurosyphilis), and Friedreich's ataxia [4].

Later techniques included sequential photography and motion pictures, or movies. Some of the earliest examples of movies of medical subjects were produced in 1885 as a collaboration between Philadelphia neurologist Francis Dercum and pioneering motion picture photographer Eadweard Muybridge. This collaboration resulted in some classic sequential images of abnormal movements in patients with neurological disease [5]. Neurologists quickly adapted the new motion capture technology to record and illustrate abnormal movements.

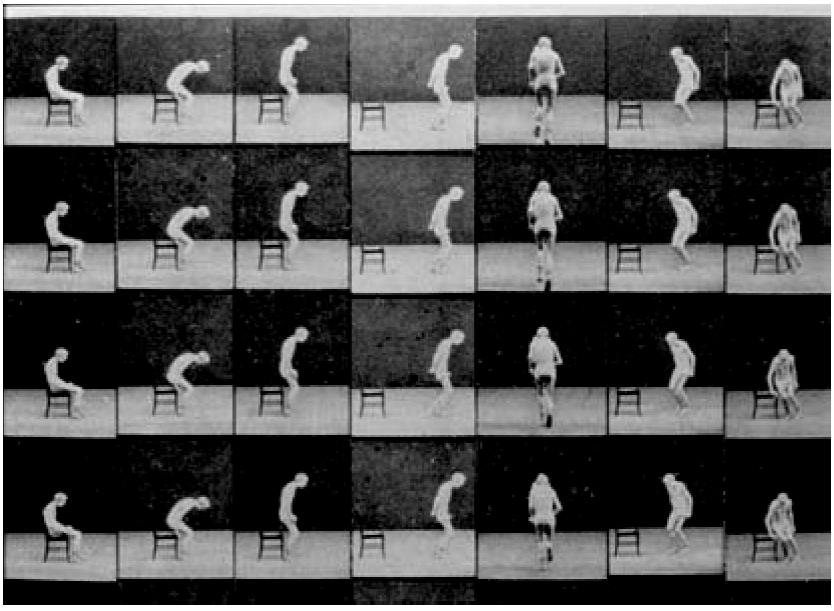

Figure 4. Early motion picture sequences of a patient with Parkinson's disease in A Text-book of Medical Diagnosis written by Anders and Boston 1911 [6].

1.2 General principles for the measurement of body movement

In clinical neurological examinations, the examiner asks the patient to perform different active and passive movements in order to evaluate clinical aspects of muscle strength, motor planning, and motor control. The results are compared with the examiner's previous experiences from examining

healthy and ailing persons, and together with the patient interview are synthesized into a clinical syndrome and a disability assessment. Although this process can take place without any use of objective measurement techniques, there is often a need to understand and evaluate longitudinal changes in symptoms and disabilities. This is particularly evident when a clinical study of drug effects or disease progression is undertaken.

The simplest way to create a measure that can be used for evaluations over time is to design a rating scale. The rating scale is an attempt to objectify the impressions gained by the examiner, by setting up more or less strict rules for grading a symptom. Rating scales introduce the possibility to reduce symptoms to nominal and numeral values, which in turn makes it possible to perform statistical calculations comparing movement disability in different patients and under different conditions. There are, however, problems with rating scales that restrict their usefulness somewhat. One is that the assessment is subjective and may vary from one investigator to another and from one time to another. Another problem is that rating scales are rarely linear. One scale level often covers a spectrum of disabilities, which reduces the sensitivity for detecting changes. Such disadvantages can be reduced but not completely eliminated, for example by validating inter- and intra-rater variability, and by ensuring that raters are blinded to therapy.

The problem of inter- and intra-rater variability, and sometimes also the problem of nonlinearity, can be solved by using objective movement measurement techniques. The following section gives a short overview of rating scales and measurement techniques along with a description of the Posturo-Locomotor-Manual (PLM) method.

1.3 Rating Parkinsonism

1.3.1 The Unified Parkinson's Disease Rating Scale (UPDRS)

After the introduction of L-DOPA for treating Parkinson's disease in late 1960s [7], the need for evaluation tools grew stronger. Many of the early scales [8, 9] were merged into the Unified Parkinson's Disease Rating Scale (UPDRS), which was introduced in 1987 [10] and is now the most widely-used rating scale for symptoms and disabilities in PD.

The UPDRS covers four domains: mentation and mood (UPDRS I), activities of daily living (UPDRS II), motor function (UPDRS III), and complications related to therapy (UPDRS IV). It assesses a total of 42 items, and the

examiner rates the symptoms and problems on a 5-point scale (and sometimes on a 2-point scale – present or not). Sometimes the different domains are used separately, and sometimes the total score is used.

In 2003, the Movement Disorder Society sponsored a critique of the UPDRS, aimed at identifying the strengths and weaknesses of the current scale. Some of the concerns raised were that the current scale might under-represent many elements of PD impairment and disabilities, and that the UPDRS was less than comprehensive in its assessment of non-motor features of the disease [11]. The revised version, MDS-UPDRS [12] has not yet replaced the previous UPDRS, and in this thesis the term "UPDRS" always refers to the version from 1987.

1.3.2 Hoehn and Yahr

Hoehn and Yahr (H&Y) is a widely used clinical staging scale for PD that was first published in 1967 [13]. It gives a more basic description of Parkinsonian disability and impairments than UPDRS III, using a five-point scale to provide a rough estimate of disease severity [14]. A recognized problem with the original H&Y is that stage II is very wide and covers a large proportion of patients. For this reason, a modified version that includes two additional stages (1.5 and 2.5) is commonly used. This revised version has not been validated clinimetrically, and so its use is not recommended by the MDS [14]. However, because the revised seven-point scale is nevertheless in wide use and recommended in the Core Assessment Program for Surgical Interventional Therapies in PD [15], it is this version that is used in this thesis.

1.3.3 Evaluation of quality of life and non-motor symptoms

Rating scales and inventories directed at patient-perceived quality of life as well as the occurrence of non-motor symptoms have recently become popular; these include the Parkinson's Disease Quality of Life Questionnaire (PDQ39) and the Non-Motor Questionnaire (NMS-QUEST). However, like the recently introduced Clinical Impression of Severity Index for Parkinson's Disease (CISI-PD) [16], these instruments will not be further discussed here as they were not used in the studies described in this thesis.

1.4 Measuring movements

1.4.1 Timed tests

The simplest objective measurement of a movement is a registration of the time taken to perform it. There are several timed tests in use for the evaluation of Parkinson's disease. The Core Assessment Program for Intracerebral Transplantation (CAPIT) protocol [17], for example, includes the stand-walk-sit test that measures the time it takes for a patient to rise from sitting in a chair, walk 7 m forward and back, and sit down again. Timed tests of hand/arm function in CAPIT include the pronation-supination test, where patients alternate between tapping their palm and the back of the hand on their lap and the time it takes to complete 20 alternating movements is registered; the finger dexterity or finger tap test, which similarly registers the time it takes to perform ten taps with the thumb and index finger; and the hand/arm movement test, which registers the number of times a patient can move their hand between two points 30 cm apart on a horizontal surface in 20s [17].

1.4.2 Activity monitors

An accelerometer measures the acceleration (including gravity) of anything that it is mounted on. Its measurement principle is to register the displacement of a mass caused by inertia when the mass is subjected to acceleration. In practical terms, the accelerometer behaves like a mass suspended on a spring on a frame, and the displacement of the mass when the frame accelerates produces a change in current, resistance, or capacitance that can be detected. To measure acceleration in more than one direction, accelerometers are mounted in biaxial or triaxial configurations.

Accelerometers can be used to measure physical activity (and energy expenditure). In patients with PD, triaxial accelerometers have been used to distinguish between medicated (ON) and unmedicated (OFF) state during daily life activities, and to study bradykinesia [18, 19], tremor [20], medication response [21], drug-induced dyskinesia [22], and motor fluctuation [21, 23]. The advantage of accelerometers is that they can be used in any location, and recordings are not restricted to a pre-defined movement pattern. Until now, however, it has been a challenge to analyze the large amount of data produced by accelerometers.

1.4.3 Motion capture systems

Motion capture systems aim to record complex movements with high fidelity. The most common way to record movements is obviously filming, which because of high fidelity is good for qualitative analysis of movement in particular movements in one plane. More quantitative information can be gained from systems that provide some sort of visual tracking, as this can be used to create virtual representations of the movement which in turn can be used for objective measurements of a large number of variables that characterize the body or object movement. Generally, motion capture refers to systems where the movement of identified points can be translated to a mathematical or virtual model.

Early motion capture systems relied on active light-emitting markers that were used to identify parts of the moving body. The marker identification was based on predefined synchronized flashing patterns, which meant that the markers had to be connected to a synchronizing unit with cables [24]. In most cases, active markers are inconvenient in bio-locomotive studies. More recent optoelectronic systems make use of passive light-reflecting markers which are illuminated by infrared light sources. Tracking of movement can also be achieved by picture analysis, which is used to identify a particular point on the body, though this is usually not as precise as marker-based identification. All image-based movement analysis for biomechanical purposes requires the identification of points on anatomical structures. After identification, the coordinates of these points are determined on successive images, thus tracking the movements of the corresponding anatomical structures. Movement analysis is based on the trajectories of these marked (or unmarked) anatomical points.

A problem with all systems that do not use active markers is the risk of misidentifying markers when the trajectories of two markers cross each other in space. Although this risk can be reduced by introducing anatomical models that restrict the possible movements a point can make, there has long been a need for manual supervision and correction of erroneous marker identification. With increased computer power, however, tracking algorithms have been improved and fully automatic systems are now widely available. This development is illustrated, for example, by the Kinect® device, which is a motion capture camera for marker-free tracking intended for the gaming industry and currently priced at about $100.

1.4.4 The Posturo-Locomotor-Manual (PLM) test

The PLM test was developed in an early attempt to use optoelectronic techniques to detect and quantify movement disorders. In this test, a predefined movement is repeated many times and recorded using motion capture technique. The principal outcome is the best average of nine consecutive movements in any session. In the development of the PLM test, several different movement patterns were evaluated [25]. The paradigm was that the movement should engage a large part of the body and reflect a naturally occurring movement that most ambulatory individuals should be able to perform. The early evaluations demonstrated that, in comparison with simple movements, a complex movement pattern consisting of a postural phase (picking up an object from the floor), a locomotion phase (walking a short distance), and a manual phase (placing the object on a raised platform) increased the difficulty more for patients with PD than for healthy controls. Treatment with L-DOPA improved motor performance in PD patients on all levels of movement complexity, but mostly in the PLM pattern and particularly in a subgroup of PD patients with advanced disease [25].

The PLM movement is short and always performed with one hand and the same side of the patient facing the cameras. The reason for this is that early systems (IROS 3D) used cable-connected active markers, which constrained the movement to a 2 x 2 x 2 m area and did not allow turning.

MacReflex system

The introduction of passive hemispherical markers coated with reflective tape and a single point light source made it possible to perform the PLM test without a marker suit connected to the camera with a cable. This simplified the procedure and allowed a broader introduction of the measurement method in patients with hypokinetic motor problems [26, 27]. At this time, tracking algorithms did not allow a fully automatic analysis, and the test administrator had to review the record of every movement to ensure that markers were not misidentified. Although this procedure could be very time-consuming, the total time for analysis was shorter than with the IROS 3D system, due to better computing capacity.

QbTestMotus

The PLM test recording has been further developed with the QbTestMotus system. This system has a fully automated tracking system and uses an online database to access the collected data. The automated target tracking algorithm uses linear prediction based on previous marker positions to find the best marker candidates in the next image sample to incorporate into the tracks.

This is combined with a body segment model to eliminate errors due to misidentification of markers when the trajectories of two markers cross [28]. The QbTestMotus implementation of the PLM test includes standardized equipment (a camera, a carpet clearly marked with correct start and platform positions) and standardized test instructions.

1.5 Parkinsonism

Parkinsonism refers to a constellation of symptoms that occur following degeneration of dopamine neurons in the dorsolateral part of the substantia nigra. This degeneration leads to decreased levels of dopamine in the putamen and caudate nucleus, and is associated with reduced ability to perform repeated alternating movements with maintained amplitude and frequency (bradykinesia), simultaneously increased muscular tone in agonists and antagonists during passive movement (rigidity), resting tremor, and impaired postural reflexes. These symptoms together form the classic Parkinson syndrome. Bradykinesia is a hallmark of basal ganglia disorders with dopamine deficiency, and is a mandatory symptom for the diagnosis of PD (unlike rigidity, tremor, and postural impairments, some of which symptoms may be absent).

1.5.1 Parkinson's disease

PD is a degenerative disorder of the central nervous system and the most common cause of Parkinsonism [29]. A definite diagnosis of PD can only be made after autopsy, as it is based on clinicopathological findings. The clinical diagnosis can therefore by definition only be possible PD or probable PD, and is based on the fulfillment of specific clinical criteria (UK PDSBB see Appendix) [30]. The motor symptoms of PD, as well as many of the non-motor symptoms, are caused by the progressive loss of dopamine neurons in the upper brainstem, but the disease is not restricted to dopamine neurons [31]. In terms of etiology, PD may be the best-characterized of all neurodegenerative disorders, and there are familial variants as well as environment factors and several known genes contributing to the pathology [32-34]. Nevertheless, most cases are sporadic and the etiology in these cases is unknown [29]. The prevalence of PD in industrialized counties is estimated at 0.3% of the general population and about 1% of the population older than 60 years [35, 36], with a mean onset in the late 50s to mid 60s [37]. However, it can occur as early as the 20s or 30s, and the less common young-onset Parkinson's disease affects 5-10% of PD patients [38, 39]. The life expectancy in PD is slightly shortened [40].

There is no cure for PD. However, with medication and neurosurgical interventions, many symptoms can be alleviated for a long time. The mainstay of pharmacological treatment includes the dopamine precursor L-DOPA, COMT and MAO inhibitors (which prolong the availability of L-DOPA and the action of dopamine), and dopamine agonists. L-DOPA is converted into dopamine in dopaminergic and serotoninergic neurons, and is the most frequently used drug to alleviate Parkinsonian motor symptoms [41].

1.5.2 Multiple system atrophy

MSA is a rare sporadic and progressive neurodegenerative disorder with adult onset and rapid progression [42]. It is characterized by varying severity of Parkinsonism, cerebellar ataxia, autonomic failure (cardiovascular and urogenital), and pyramidal tract symptoms [43-46]. The disease affects both sexes equally, and onset is usually in middle age. MSA has a more rapid progression than PD, with a mean survival of 9.3 years from the first symptoms [47, 48]. In male patients, one of the first signs might be erectile dysfunction, which often precedes bladder dysfunction as an early sign of MSA [49, 50]. MSA can present with predominantly or exclusively cerebellar (olivopontocerebellar atrophy, MSA-C) or Parkinsonian (striatonigral degeneration, MSA-P) manifestations in combination with progressive autonomic failure. The most common feature of MSA-C is ataxia of gait, often accompanied by ataxia of speech and cerebellar oculomotor dysfunction [51].

In its early stages, MSA-P can be very difficult to differentiate from PD, as the motor signs include bradykinesia, rigidity, and gait impairments, all of which are typical of PD. However, although up to 30% of MSA-P patients show a clinically significant response to L-DOPA at some point [44], this response usually vanishes within 5 years [48, 52]. If tremor is present, it is usually irregular and postural; the classical pill-rolling Parkinsonian rest tremor is uncommon [53].

1.5.3 Progressive supranuclear palsy

Progressive supranuclear palsy (PSP) is a rare progressive degenerative brain disorder which is sometimes dominated by asymmetric bradykinesia and rigidity , often with a moderate initial respons to levodopa. This type of PSP with Parkinsonism can be very difficult to distinguish from PD at early stages of disease [54, 55]. After PD, PSP is the most common syndrome with Parkinsonism. The onset is usually between 60 to 65 years of age, and the median survival is 6 to 7 years [56]. PSP is somewhat more common in men

than in women [57]. One cardinal symptom is postural instability, which often leads to unexplained falls within the first year of disease [58]. The other cardinal symptom of PSP is supranuclear vertical gaze palsy, which may take 3 to 4 years to develop [59]. These two symptoms are the main inclusion criteria for the diagnosis of probable PSP under the modified diagnostic research criteria published by the National Institute of Neurological Disorders and Stroke Society for PSP diagnostic research criteria) [57, 60]. Other clinical characteristics of PSP are frontal cognitive impairments, axial rigidity, speech and swallowing difficulties (pseudobulbar palsy), and L-DOPA unresponsive Parkinsonism [61].

1.6 Diagnostic difficulties in patients with Parkinsonism

There is a large overlap between the signs and symptoms of different forms of neurodegenerative diseases that involve the basal ganglia [62, 63], and it can be difficult to differentiate between patients with Parkinsonism in the early stages of disease. The most widely used clinical criteria for diagnosing PD are those introduced by the UK Parkinson's Disease Society Brain Bank (UKPDS BB) [30, 64], which provide three strategies for the diagnosis of probable PD: signs that must be present, signs that should not be present, and supportive criteria [64]. The diagnosis of probable and possible MSA is also clinical, following diagnostic guidelines known as the MSA diagnostic criteria [44, 65]. Diagnostic guidelines provided by the National Institute of Neurological Disorder and Stroke and the Society for PSP (NINDS-SPSP) are also available for the diagnoses of probable and possible PSP [57, 60]. The definite diagnosis of PD, MSA, or PSP can only be confirmed at autopsy.

Diagnostic accuracy has increased with the use of strict clinical criteria by movement disorder specialists [64, 66, 67], but revisions of the clinical diagnosis in patients with Parkinsonism are not uncommon even when the initial diagnosis is made by a movement disorder specialist. Considering the substantial difference between these disorders in regard to disease progression and therapy effect, it would be desirable to have evaluation tools that can accurately differentiate between the different diseases, follow progression, and evaluate therapy effects.

1.7 The L-DOPA responsiveness test

Although current guidelines suggest that L-DOPA responsiveness can be evaluated after a 2-3 month treatment trial [68, 69], acute dopaminergic challenge tests are not recommended as diagnostic tools in PD [70, 71]. This does, however, not preclude their use in research and in clinical evaluations of interventions aimed at improving motor function. There are several potential pitfalls in evaluating a patient's acute response to L-DOPA. No consensus operational definition exists of how large the improvement must be for it to be considered a positive L-DOPA response, how much L-DOPA should be given, and for how long [72]. Different cut-off values for UPDRS improvements have been suggested for categorizing patients as L-DOPA responsive or not. A decrease of more than 5 points in UPDRS III after L-DOPA administration represents a clinically relevant improvement in motor ability [73, 74]. Still others have defined responders as those whose UPDRS III scores improve by at least 30% [75, 76]; however, the outcome then largely depends on baseline UPDRS scores, so that more advanced patients have lesser probability of demonstrating a positive effect. In the core assessment program for surgical interventions [15], a 33% decrease in UPDRS III is considered a positive test. With short "timed tests" it can be easier to perform repeated measurements during defined treatment conditions and thereby obtain data that can be statistically analyzed within the same patient. This is how L-DOPA response is evaluated using the PLM method.

1.8 rTMS

In Study IV, the non-invasive method of repetitive transcranial magnetic stimulation (rTMS) was used to stimulate nerve cells in superficial areas of the brain [77]. rTMS works by producing a rapidly changing magnetic field that induces an electrical current in tissues at a short distance from the stimulation coil. The current excites inhibitory and excitatory cortical neurons [78, 79]. The direct effect of rTMS takes place superficially in the brain, but the effect of altered neurotransmission in the communication with other parts of the brain can produce conditioning effects in distant cortical [80] or subcortical areas such as the basal ganglia [81-83]. A large number of studies have explored the effect of rTMS on the human cortex, demonstrating that rTMS can modulate cortex excitability beyond the time of stimulation [84] and change the release of dopamine in the striatum [85]. The effect of rTMS on cortex excitability is influenced by the stimulation settings [86]. It is generally assumed that high-frequency stimulation ($\geq$5 Hz) produces a local increase in cortical excitability and low-frequency stimulation

(0.1-1.0 Hz) has an inhibitory effect [87]. Stimulation settings may therefore be critical for the outcome.

2 AIM

The purpose of this thesis was to evaluate the validity, reliability, and discriminatory ability of the Posturo-Locomotor-Manual (PLM) test, an objective optoelectronic measurement system; and further to use the PLM test as an objective measure in a clinical experimental study. The main questions addressed were:

- Is the quality of the PLM test preserved when the movements are tracked using an automated software tracking method, QbTestMotus, instead of semi-automatic and manually corrected tracking?
- Is there a correlation between the objective optoelectronic PLM test and the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS III)?
- Is the PLM test a reliable method?
- Does the PLM test discriminate between healthy controls and patients with Parkinsonism?
- Does the PLM test differentiate between patients with PD and the atypical Parkinsonism diagnoses MSA and PSP?
- Could the PLM method be used as a research tool to measure changes in movement capacity after treatment interventions in the early stages of PD?

3 METHODS

3.1 Ethical considerations

All study designs were approved by the regional Ethical Review Board in Gothenburg, Sweden (refs: 377-09, t826-12, and s641-03). Patients included in the retrospective studies (Studies II and III) had given informed consent to the testing procedure and to saving of anonymous data for future research use. Healthy controls in Study III and patients in Studies I and IV gave informed consent to the study protocol prior to the PLM test, in accordance with the declaration of Helsinki [88].

3.2 Recruitment

3.2.1 Inclusion criteria

Inclusion criteria for all patients were age between 30 and 80 years, and the presence of a Parkinsonian syndrome. PD was defined using UK PDSBB research criteria [30, 64], MSA using the criteria proposed by Gilman [44], and PSP using the criteria proposed by Litvan [60]. In Study IV, we used the additional inclusion criterion of a decrease in UPDRS III of at least 2 points after administration of the patient's ordinary morning medication. The inclusion criterion for the control group in Study III was age between 30 and 80 years.

3.2.2 Exclusion criteria

Exclusion criteria for the patients were the presence of other central nervous system diseases, hereditary diseases, and treatment with neuroleptics. Exclusion criteria for the control group were active medical illness, and history of past or current neurological disease.

3.2.3 Recruitment procedures

All patients were recruited from the Movement Disorders Clinic at Sahlgrenska University Hospital, Gothenburg, Sweden. All had been clinically diagnosed by one of the clinic's movement disorder specialists, and all had been referred to the movement laboratory to perform a PLM test as part of clinical routine.

Study I included patients referred to perform a PLM evaluation between April and December 2006. Study II included patients scheduled to perform both the PLM L-DOPA test and UPDRS ratings in the same session between 1999 and 2010. Study III included patients fulfilling the diagnostic criteria for a probable or possible diagnosis (PD, MSA or PSP) and scheduled for a PLM L-DOPA test. The healthy controls were recruited from hospital staff, the local patients' association, and relatives of the PD patients. For Study IV, 12 early-stage PD patients were recruited in the spring/summer of 2006 by senior neurologists specializing in PD.

3.3 Diagnoses, demographics, and study design

3.3.1 Study I

This prospective study included 61 patients: 32 with probable PD, 7 with possible PD, 7 with atypical PD, 9 with basal ganglia disease, 1 with essential tremor, and 5 with other neurological disorders. 44 men and 17 women aged 64.2 ± 10.7 years (mean ± SD).

3.3.2 Study II

This retrospective study included 73 patients with Parkinsonism: 47 with PD, 17 with MSA, and 9 with PSP 9. The patients' characteristics are presented in Table 1.

Table 1. *Descriptive data for patients in Study II.*

Diagnosis	PD (n=47)	MSA (n=17)	PSP (n=9)
Age (*mean ± SD, range*)	61.9±7.2 (52-76)	53.9±9.0 (43-68)	64.7±10.4 (44-75)
Males/females	29/18	12/5	7/2
Hoehn & Yahr $_{ON}$ *(median, range)*	2.5, 1-3		
UPDRS $_{OFF}$ (mean±SEM, range)	35.7±1.7, 6-59	31.6±3.1, 15-61	32.7±2.6, 17-46
UPDRS $_{ON}$ (mean±SEM, range)	19.1±1.7, 2-61	29.7±3.1, 13-60	29.8±7.0, 18-44
MT $_{OFF}$ (mean±SEM, range).	3.5±0.4, 1.6-19.3	3.8±0.6, 1.8-10.6	8.6±3.9, 2.6-38.7
MT $_{ON}$ (mean±SEM, range).	2.1±0.1, 1.2-4.5	3.6±0.5, 1.7-8.7	7.9±3.25, 1.8-30.8
Symptom duration[1] (*mean ± SD*)	13.1±5.7	3.4±2.1	4.0±3.6
Treatment (*mg LED*, mean ± SD*)	1258 ± 605	492± 525	494 ± 578

*L-DOPA equivalent dose calculated according to Tomlinson et al. [89],
[1] Patient reported duration of symptoms.

3.3.3 Study III

In Study III, 132 patients with intermediate to advanced stages of Parkinsonism: 56 with PD, 53 with MSA comprising 42 with MSA-P and 11 with MSA-C, and 23 with PSP were retrospectively included along with 37 prospectively included healthy controls. The patients' characteristics are presented in Table 2. Among these, 21 of the PD patients, 17 of the MSA patients, and 9 of the PSP patients were also included in Study II.

Table 2. *Descriptive data for patients in Study III.*

Diagnosis	PD (n=56)	MSA (n=53)	PSP (n=23)	Healthy (n=37)
Age*	60.9±9.5	60.8±9.4	67.6±6.7	61.7±9.7
male/females	34/22	34/19	16/7	8/29
$H\&Y_{ON}$**	2.5 (1-4)	2.9 (1-4)	3.3 (2.5-4)	
Symptom duration*,[1]	11.1±6.7	4.1±2.8	4.2±3.0	

H&Y, Hoehn and Yahr staging scale, * mean, SD, **median (range)
[1] Patient reported duration of symptoms.

3.3.4 Study IV

This prospective study included 10 right-handed patients (6 men, 4 women) with early-stage PD, aged 57.0 ± 8.9 years (mean ± SD; range was 39–67 years), with symptom duration of 4.2 ± 2.9 years (mean ± SD), mean $H\&Y_{ON}$ of 2.2 (range: 2–2.5), and a daily L-DOPA equivalent dose (LED) [89] of 674 ± 316 mg (mean ± SD). Descriptive data for these patients are given in Table 3, and their ordinary morning medication is presented in Table 4. Of the twelve patients recruited to the study, one was excluded due to a lack of significant medication response when tested in the study situation, and another declined to continue the study after the first session due to experiencing aggravation of symptoms. This patient received sham stimulations only.

Table 3. *Descriptive data for the patients in Study IV.*

ID	Gender	Age	Duration	$H\&Y_{ON}$	Stimulated side	Morning LED*	Daily LED*
1	M	65	6	2	L	334	934
2	M	49	6	2	R	236	808
3	F	68	3	2	L	150	600
4	M	39	2	2.5	L	200	800
5	M	60	1	2	R	200	500
6	M	54	9	2.5	L	183	998
7	F	57	7	2	L	169	978
8	F	59	1	2	L	36	108
9	F	53	1	2.5	L	100	200
10	M	67	6	2	R	267	816

*LED, L-DOPA equivalent dose [89]

Table 4. *Patients' ordinary morning medication in Study IV.*

1	2 mg Cabergoline; 200/50 mg (Levodopa / Carbidopa)
2	200/50 mg (Levodopa/Benserazide); 0.36 mg Pramipexole
3	150/62.5 mg (Levodopa/Benserazide)
4	200/50 mg (Levodopa/Benserazide)
5	200/50 mg (Levodopa/Benserazide)
6	100/25/200 mg (Levodopa/Carbidopa/Entacapone); 5 mg Bromocriptine
7	100/25/200 mg (Levodopa/Carbidopa/Entacapone); 0.36 mg Pramipexole
8	0.36 mg Pramipexole
9	100/25 mg (Levodopa/Benserazide)
10	100/25/200 mg (Levodopa/Carbidopa/Entacapone); 2 mg Cabergoline

3.4 Assessments

3.4.1 The PLM test

The PLM movement begins with the participant standing erect at the starting position with their feet together. At a signal, they are asked to pick up the object from the floor, walk forward, and place the object on a stand located 1.5 m away at chin height. Reflective ball markers, 4 cm in diameter, are attached to the patient's head, shoulder, arm, hip, calf, and the contralateral foot of the most affected side of the body (if both sides are equally affected, the markers are attached to the dominant side). A seventh marker is located on the test object, which consists of a 500g metal handle on a base plate (fig. 5). The marker positions are registered in two dimensions in the sagittal plane of the participant, with a sampling frequency of 50 Hz and a spatial resolution of 1:23 000 in the horizontal full view and 1:18 000 in the vertical full view. The PLM movement phases are recognized by the software from the velocity profiles of the ball markers [26, 90, 91].

Definition of the PLM variables

Movement time (MT) is defined as the time taken for the object to move from the floor to its final resting position on the stand (Fig. 5) The postural phase (P) is defined as the time taken for the head to rise from its lowest to its highest position during the movement, measured from the moment when the head starts to move upwards or the object leaves the floor, whichever comes first. The locomotion phase (L) is defined as the time taken for the forward locomotion, starting when the leg or foot markers begin to move forward in the horizontal direction and ending when both feet are finally still or when the object is placed on the stand, whichever comes first. The manual phase (M) measures the time spent in the goal-directed arm movement, starting from the first increase in the angle between an imaginary line through the shoulder and elbow markers and another imaginary line through the shoulder and hip markers. The M phase is considered to end when the object is positioned on the stand. The overlap of the movement phases is described using the simultaneity index (SI) as follows: SI = (P+L+M)/MT (Fig. 5). The PLM movement is performed three times in immediate succession for each measurement; this triplet of PLM movements forms one measurement group.

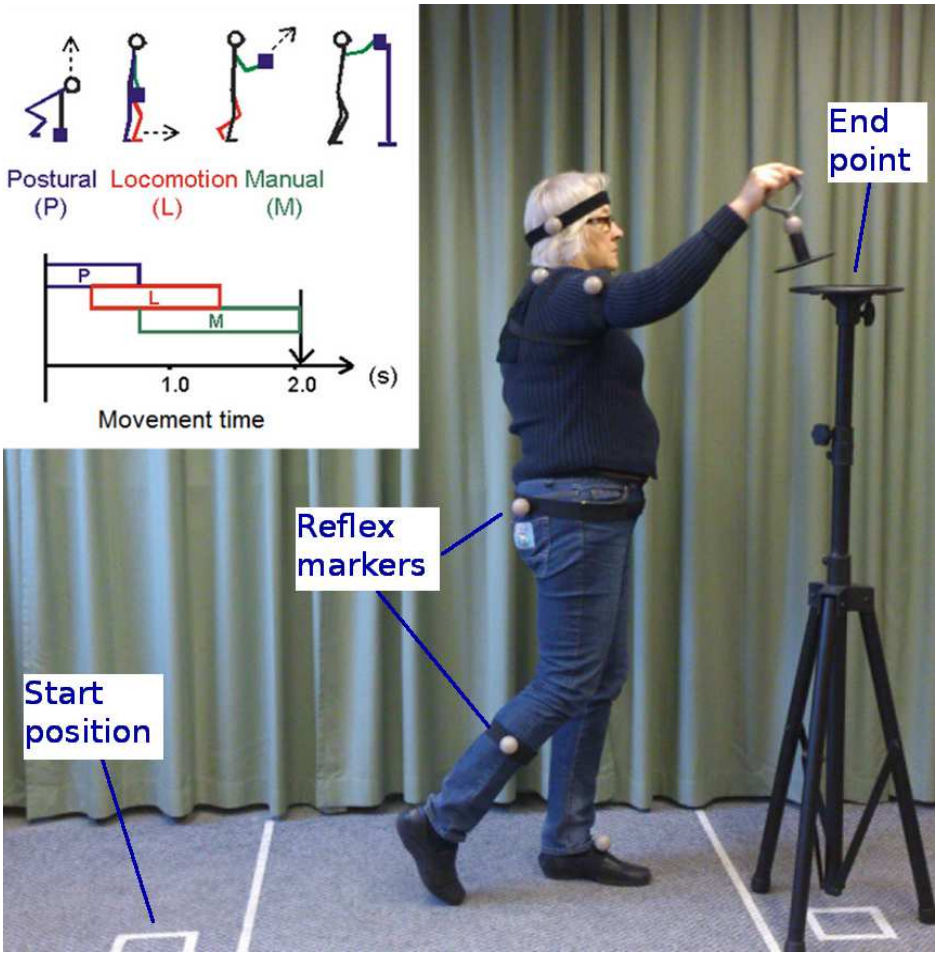

Figure 5. The stick figure demonstrate the PLM movement pattern with the different PLM phases MT, P, L, and M. The SI (how simultaneous the patient is doing the movement) is calculated by (P+L+M)/MT = SI and is illustrated in the graph beneath the stick figure. The photo shows the position of the six reflex markers, the walk distance and the start and end position of the object.

3.4.2 UPDRS III

UPDRS III involves 14 physician/physiotherapist-rated items covering a wide range of motor performance and scored on a coarse-grained scale from 0 to 4 with a total sum score of 108. A clinical evaluation is made of normal performance (0); mild (1), moderate (2), or severe (3) impairment; or incapacity to perform the task (4) [92]. The evaluation includes both upper and lower extremities as well as right and left side and includes items such as rest tremor, action tremor, rigidity, bradykinesia, gait, and posture (Table 5).

Table 5. *UPDRS III items.*

Item 18	speech	
Item 19	facial expression	
Item 20	resting tremor	including head and extremities
Item 21	postural tremor	assessment of hands
item 22	rigidity	including head and extremities
Item 23	finger taps	taps of thumb with index finger
Item 24	opening and closing the fist	rapid movement of the hand
Item 25	pronation and supination	rapid alternating movements of the hand
item 26	leg agility	rapid heel tapping
Item 27	arising from a chair	
Item 28	posture	
Item 29	gait	
Item 30	postural stability	Pull test
Item 31	bradykinesia/hypokinesia	

UPDRS III subdomains (Studies II and IV)

In Study II, we divided UPDRS III into subdomains that would reflect aspects of the PLM variables MT, P, L, and M. None of the PLM variables measure speech, facial expression, resting tremor, or postural tremor, so a subdomain was constructed with these scores removed: UPDRS (-). The postural subdomain consisted of items 27-28, 30, the leg subdomain of items 26 and 29, and the hand/arm subdomain of items 23-25 (from the most affected side). Items 27-30, which reflect Postural Instability and Gait Difficulties (PIGD), made up the PIGD subdomain. Neck rigidity, leg rigidity, and hand/arm rigidity each made up its own subdomain (Table 6).

Table 6. *UPDRS III subdomains in Study II.*

PIGD * (postural domain + gait)	Item 27	arising from a chair
	Item 28	posture
	Item 29	gait
	Item 30	postural stability
Postural domain	Item 27	arising from a chair
	Item 28	posture
	Item 30	postural stability
Rigidity neck	Item 22	neck
Leg domain	Item 26	leg agility
	Item 29	gait
Rigidity leg	Item 22	leg
Hand/arm domain **	Item 23	finger taps
	Item 24	opening and closing the fist
	Item 25	pronation and supination
Rigidity arm**	Item 22	arm

*Postural instability gait difficulties

** Most affected side

In Study IV, we were interested in evaluating the effects of rTMS. We stimulated the hand motor cortex contralateral to the most affected side. The effect on the PLM movement parameters was expected to occur in the most affected side, and most likely in the upper extremity. Total UPDRS III was therefore also divided into three subdomains that might reflect effects from the rTMS: hand/arm domain (most affected side and best side), leg domain (most affected side and best side), and other (Table 7).

Table 7. *UPDRS III subdomains in Study IV.*

Hand/arm domain	Item 20	resting tremor in the arm
	Item 22	rigidity in the arm
	Item 23	finger taps
	Item 24	opening and closing the fist
	Item 25	pronation and supination
Leg domain	Item 20	resting tremor in the leg
	Item 22	rigidity in the leg
	Item 26	leg agility
	Item 27	arising from a chair
	Item 29	gait
Other	Item 18	speech
	Item 19	facial expression
	Item 20	resting tremor in the neck
	Item 21	postural tremor
	Item 22	rigidity in the neck
	Item 28	posture
	Item 30	postural stability
	Item 31	bradykinesia/hypokinesia

3.5 The L-DOPA test

3.5.1 The PLM test

Initially, participants were instructed to do the PLM movement at their own pace in order to get used to the motion. After the third group, the patients were asked to perform the task as quickly as possible until a total of 10 baseline groups had been collected. During these ten groups, most patients reached a performance plateau. The mean MT, P, L, and M durations (s), as well as SI, were automatically calculated using the three fastest consecutive groups of PLM measurements to define the best mean OFF (MT_{OFF}) performance (Fig. 6). All nine individual measurements in these groups were used to calculate standard deviations for each variable.

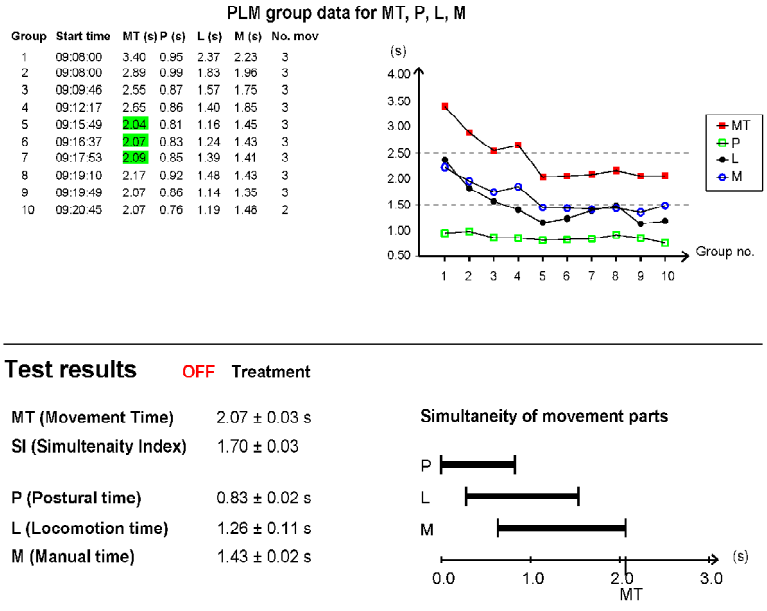

Figure 6. Example of baseline PLM performance before L-DOPA administration in a PD patient (OFF).

When baseline performance had been determined, the patients were given 200 mg of L-DOPA (Dispersible Madopar® Roche, Basel, Switzerland) dispersed in a glass of water [69]. Approximately 30 minutes after the administration of L-DOPA, the measurements were resumed and two consecutive groups of PLM measurements were collected every 10 minutes for the next 90 minutes.

This method was chosen to ensure that measurements were obtained at the time of maximum L-DOPA concentration [93, 94]. The three fastest consecutive groups of measurement after L-DOPA administration were designated best mean ON (MT_{ON}) performance (Fig. 7).

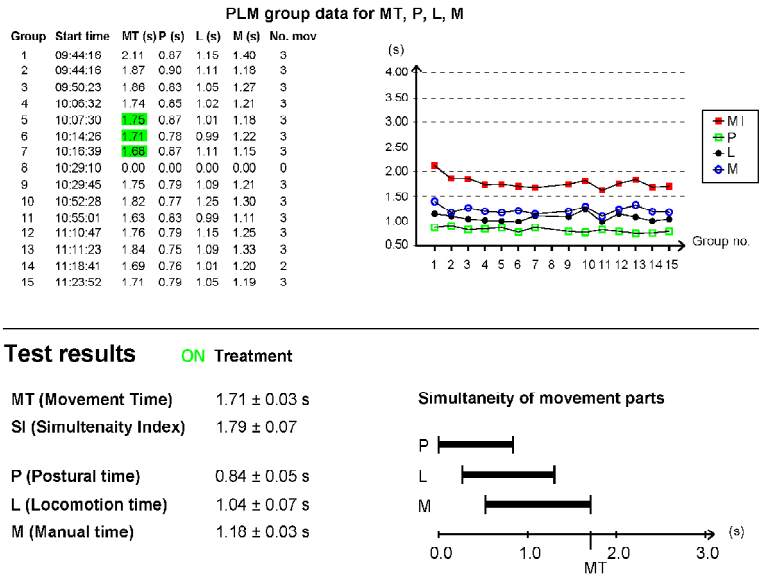

Figure 7. Example of PLM performance after L-DOPA administration in a PD patient (ON).

A significant positive L-DOPA response was defined as an improvement in MT where the confidence interval for MT_{ON} ($MT_{ON} \pm 1.96$ SD) was numerically lower and disjoint from the confidence interval for MT_{OFF} ($MT_{OFF} \pm 1.96$ SD).

3.5.2 UPDRS III

In Studies II and IV, evaluation of the motor part of the UPDRS was performed as described by Goetz et al. [95]. In study II evaluation was made before (UPDRS III_{OFF}) and about 60-70 minutes after (UPDRS III_{ON}) administration of 200 mg of L-DOPA (Madopar®, 200 mg). Only scores from the most affected side were used. A positive L-DOPA response was defined as an improvement in UPDRS III score of 6 or more points.

3.6 rTMS

Biphasic rTMS pulses were delivered through a figure-of-eight coil (MCF-B65) attached to a MagPro X100 (Medtronic). Sham rTMS was performed with a commercially available figure-of-eight coil (MCF-P-B65, Medtronic); this sham coil has the same appearance and provides the same noise as the real rTMS coil. On each study day, four sessions of 2000 rTMS pulses (10Hz) were applied over the hand motor cortex contralateral to the more severely affected upper limb (stimulations 1–4 in Figure 10). The resting motor threshold, which was determined for each individual prior to the rTMS sessions, was defined as the lowest stimulus intensity that elicited a muscular contraction from the contralateral abductor pollicis brevis muscle. The stimulation intensity was set at 90% of the resting motor threshold. The coil was held in a fixed position by a mechanical arm over the motor cortex, and a constant coil position was continuously monitored for the duration of the treatment. The patients were seated comfortably in a chair with armrests and headrest.

3.7 Procedures

PLM measurements and UPDRS ratings were all performed in the same clinical movement laboratory at Sahlgrenska University Hospital, Gothenburg, Sweden. The same trained biomedical analyst instructed all patients and administered the PLM tests. UPDRS ratings were performed by a physiotherapist specializing in movement disorders. For all studies, anti-Parkinson medication was stopped 12 hours prior to performing the L-DOPA test (evaluated with PLM test and UPDRS III rating) in accordance with published guidelines [96]. For patients in Study I who were scheduled to perform the PLM measurement in a medicated state, only ON measurements were performed.

3.7.1 Study I

The tests were performed with both test systems, PLM Test and QbTestMotus, run in parallel; data were thus collected simultaneous. Patients performed the PLM method as described in section 3.4.4. Patients were scheduled either for an acute L-DOPA test, or for a single measurement (10 measurement groups) in medicated state or as a follow-up after deep brain stimulation surgery (10 measurement groups ON medication ON stimulation, 10 measurement groups OFF medication ON stimulation, and if possible measuring groups OFF medication and OFF stimulation).

3.7.2 Study II

The acute L-DOPA PLM test and the UPDRS rating were performed as described in sections 3.4.2 and 3.5.1. Both evaluations were performed on the same occasion, both OFF and ON medication (Fig. 8).

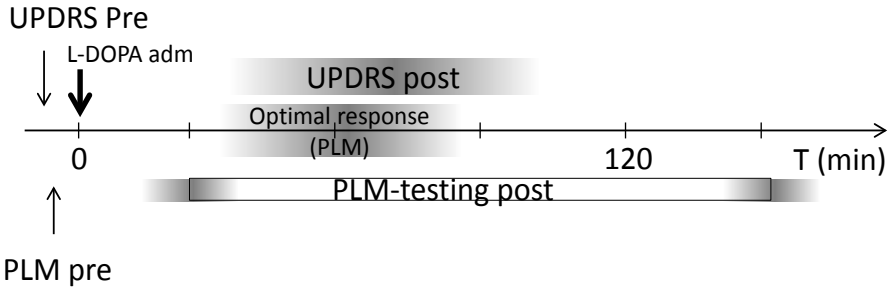

Figure 8. Timeline for Study II.

3.7.3 Study III

The patients performed the PLM L-DOPA test as described in section 3.5.1. The healthy controls performed ten baseline groups of measurements (PLM_1) where the three fastest consecutive baseline groups of measurement were registered as MT_1, P_1, L_1, M_1, and SI_1. After 90 minutes of rest, another ten consecutive groups of measurement (PLM_2) were collected, and the three fastest consecutive groups of measurement were registered as MT_2, P_2 L_2, M_2, and SI_2. No medication was administered (Fig. 9).

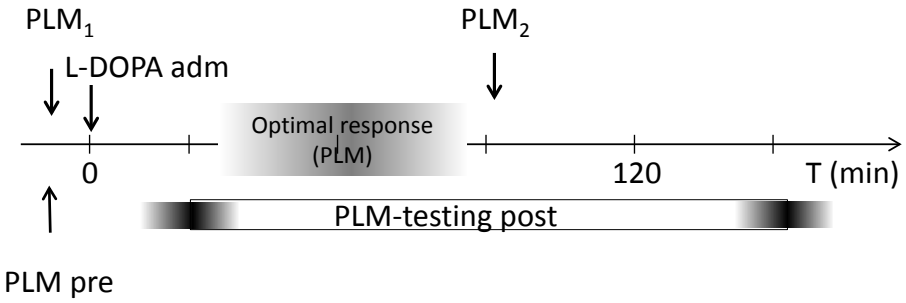

Figure 9. Timeline for Study III.

3.7.4 Study IV

All participants made two visits separated by one week. Four sessions of sham rTMS stimulations were administered on the first visit, and four sessions of active rTMS stimulations on the second. Patients arrived at the movement laboratory at 8.30 am, and after determining the individual motor threshold, measurements with the PLM test as well as scorings with UPDRS III were obtained (OFF medication). Two sets of sham/active rTMS were administered, each followed by UPDRS III/PLM measurements. After the third evaluation, the patients were given their ordinary morning medication (Table 5) and 15-30 minutes later lunch was served. A new UPDRS III/PLM test was performed 75 minutes after administration of medication, then two sets of active rTMS/sham rTMS were given, each followed by UPDRS III/PLM evaluation (Fig. 10).

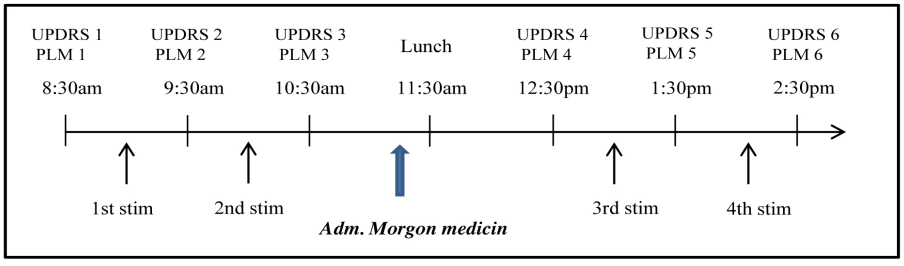

Figure 10. Timeline for Study IV.

4 DATA ANALYSIS AND STATISTICS

4.1 Statistics

Mean, SD, SEM, median, and range of data were used for descriptive purposes. All p-values were two-tailed in all studies, and a p-value of < 0.05 was considered significant.

4.1.1 Study I

Pearson coefficients of correlation were calculated, correlating each variable of the PLM test to the corresponding variable in QbTestMotus. The mean difference, SD, and 95% confidence intervals between the tested variables were calculated and a paired t-test was used to check for significant systematic differences.

4.1.2 Study II

All correlation analysis was performed using Spearman's non-parametric correlation coefficient. Fair, good, and excellent correlation was defined as r^2 of 0.25-0.49, 0.5-0.74, and $\geq$0.75, respectively [97]. Agreements between UPDRS III and the PLM MT L-DOPA tests were tested with the non-parametric McNemar's test after categorizing the response as positive or negative. Analysis of UPDRS III and PLM results at the level of diagnostic groups was done with two-way ANOVA, with diagnosis and treatment state as independent factors and UPDRS III or PLM as the dependent variables. Post hoc comparisons were Bonferroni corrected.

4.1.3 Study III

The comparison between healthy controls and patients with Parkinsonism was performed by examining the first measurements in healthy controls (MT_1, P_1, L_1, M_1, SI_1) and the corresponding PLM variables before administration of L-DOPA in patients (MT_{OFF}, P_{OFF}, L_{OFF}, M_{OFF}, SI_{OFF}). To evaluate the reliability of the PLM test, intraclass correlation coefficients (ICC) were calculated between the first and second tests performed by healthy controls (test-retest analysis). The Wilcoxon signed-rank test was used to investigate whether there was a significant difference between the first and second test in any of the PLM variables for the healthy controls. The Mann-Whitney test was used to evaluate group differences in individual PLM variables, and Fisher's exact test was used to test differences in gender distribution between groups.

Logistic regression analyses were carried out to determine how well each PLM variable differentiated between healthy controls and patients with Parkinsonism, between PD patients and patients with atypical Parkinsonism, or between patients with MSA and those with PSP. In the logistic regression analyses comparing healthy controls and patients with Parkinsonism, gender was included as an independent factor to adjust for the demographic differences. PLM variables that contributed significantly in the logistic regression analysis were combined pairwise, using stepwise forward multiple logistic regressions, to find the combination of variables that yielded the highest Area Under the Curve (AUC). Maximum likelihood estimates of the associated beta coefficients, intercept, and corresponding p-values were calculated. The sensitivity and specificity obtained from the different models were used to plot ROC (Receiver Operating Characteristic) curves and to calculate the corresponding AUC. An AUC of 1 indicates a perfect ability to classify the groups correctly.

4.1.4 Study IV

The primary outcome was change in total UPDRS III and/or changes in the PLM methods variable MT after rTMS and after administration of the patient's regular antiparkinsonian morning medication. The secondary outcomes were the changes in UPDRS III subscores (hand/arm, leg, and other) or P, L, M, or SI variables of the PLM method. UPDRS III scores and PLM data were compared using Wilcoxon signed-rank test.

5 RESULTS, COMMENTS, AND DISCUSSION

5.1 Is the quality preserved in the automated software tracking?

The aim of Study I was to ensure that measurement quality and accuracy were preserved in the new fully automated tracking implementation of the PLM test, the QbTestMotus. There was an excellent correlation between the two systems for all investigated variables (MT 0.99, P 0.946, L 0.985, and M 0.988). However, there was a significant difference between the two test methods that was seen in all variables, indicating a systematic difference between the two measuring systems (Table 8).

Table 8. *Calculation of differences between the PLM test and the QbTestMotus.*

Variable	Mean difference (s)	(95% CI)	SD
MT	0.04***	(0.03 – 0.05)	0.05
P	0.029***	(0.02 – 0.04)	0.07
L	-0.039***	(-0.05 – -0.03)	0.07
M	-0.023**	(-0.03 – -0.01)	0.07

*** $p<0.001$, ** $p<0.01$

To further investigate the relevance of these systematic differences and to analyze whether the difference had any clinical implication, the amplitudes of the systematic differences were compared to the mean differences between MT_{OFF} and MT_{ON} from positive L-DOPA tests (the L-DOPA response). The mean decreases in MT in the positive L-DOPA responders were 0.47s ± 0.30 as compared to the systematic difference of 0.04s. The absolute mean MT_{OFF} was 3.03s ± 1.30 and the absolute mean MT_{ON} was 2.56s ± 1.04 (mean ± SD). In this context, the systematic difference between the systems is negligible and most likely of no clinical relevance. Within the same measuring system there would be no discrepancy. The magnitude of the systematic difference compared to the clinically relevant differences in positive L-DOPA responders ensures that it is safe to make comparisons between data collected with the old PLM system (MacReflex system) and data collected with the new implementation.

One shortcoming of the old (MacReflex) version of the PLM method is the time-consuming post-test analysis. This included several manual signal-processing steps, which could take up to an hour to perform. By taking advantage of recent technological advances, the new implementation addresses these shortcomings by providing a fully automated tracking system and an online database giving access to the collected data; this dramatically reduces the amount of manual work required of administrators.

The QbTestMotus system has however one shortcoming; if an unlikely event occurs where the patient's movement pattern is so disturbed that the automated tracking system cannot correctly track the marker; there is no possibility for the test administrator to correct this. In the previous version, the test administrator was able to correct issues with marker tracking, while with QbTestMotus, the QbTech support staff are required to assist.

5.1.1 Conclusions

The quality of the PLM test is preserved in the new automated implementation, and it can be considered safe to use and compare data collected in the two different systems.

5.2 Correlations between the PLM method and UPDRS III

Study II investigated the correlation between UPDRS III and the PLM test. Fair to good correlation was found between most UPDRS III subdomains and the corresponding PLM variables, with a somewhat stronger correlation in ON in the full dataset (PD, MSA, and PSP). The exceptions were the M variable and the corresponding constructed UPDRS III domains (hand/arm domain and arm rigidity), where no or very weak correlation was found (Table 9).

Table 9. *Correlations between PLM variables and UPDRS III subdomains for all patients.*

	OFF			ON			OFF-ON		
	r	**p-value**	**n**	**r**	**p-value**	**n**	**r**	**p-value**	**n**
MT vs. UPDRS (total)	0.37	0.0017	70*	0.58	<0.0001	73	0.60	<0.0001	70*
MT vs. UPDRS (-)	0.35	0.0042	64**	0.56	<0.0001	66**	0.58	<0.0001	64**
P fas vs. P domain	0.36	0.0030	64	0.65	<0.0001	66			
L fas vs. Leg domain	0.51	<0.0001	64	0.64	<0.0001	66			
M fas vs. hand/arm domain***	**0.09**	**0.4925**	**64**	**0.29**	**0.0172**	**66**			

* The PLM results for three PD patients in OFF were omitted from the correlation analysis due to freezing of gait. ** UPDRS III subscores were not available for all patients. *** Most affected side.

There were fair and significant correlations between UPDRS III and PLM MT in PD patients in both OFF and ON states. Low or weak correlations were found between the two assessment tools for MSA and PSP patients (Table 10).

Table 10. *Correlation between PLM MT (s) and the total UPDRS III for each diagnostic group.*

	OFF			ON			OFF-ON		
	r	**p-value**	**n**	**r**	**p-value**	**n**	**r**	**p-value**	**n**
PD	0.47	0.0013	44*	0.44	0.0019	47	0.47	0.0015	44*
MSA	0.49	0.0448	17	0.46	0.0635	17	0.05	0.8544	17
PSP	0.27	0.4860	9	0.22	0.5755	9	0.75	0.0210	9

* The PLM results for three PD patients in OFF were omitted from the correlation analysis due to freezing of gait.

Comparison between objective monitoring measures and subjective clinical ratings is obviously complicated, and the degree of correlation between the two evaluation methods may appear modest in places. A perfect correlation between UPDRS III and the PLM test would indicate that the PLM test does not add any new information, meaning that it could be argued, not concidering other aspects of the different methods, that it would be wiser to use the cheaper and more practical rating scale. With the opposite scenario — no or very low correlation — the question would be whether the PLM test had any validity in measuring motor symptoms in patients with

Parkinsonism. Establishing a fair correlation could be considered a clinically useful validation of the quantitative PLM method.

There are several differences between UPDRS III and the PLM test. In particular, UPDRS III measures some motor features that go undetected in the PLM test, like tremor, speech, and facial expression. The presence of tremor makes up about 20% of the total UPDRS III scores, whereas it has no practical effect in PLM. Nevertheless, removing tremor and facial features from UPDRS III, (UPDRS(-)) did not improve the correlation (Table 9).

We hypothesized that the pendulous arm movement of the M variable might correspond better to arm rigidity than to hand bradykinesia, and that there would be a better correlation between the L phase and the leg rigidity score. However, this assumption was not supported by the correlation analysis.

We have shown that the M variable and the hand/arm items of UPDRS III do not correlate, and it is evident that they measure different aspects of hand/arm function in patients with Parkinsonism. The PLM method measures one continuous arm movement (moving the object from the floor to the stand) on the most affected side, whereas UPDRS III measures short repeated movements and the patient's ability to maintain movement frequency and amplitude (bradykinesia) in repeated pronation/ supination of the hand, finger tapping, and opening and closing the fist. This might be the explanation for the lack of correlation between the arm/hand domain of UPDRS III and the M variable in the PLM test. In the evaluation of a PLM L-DOPA test, the M variable is often disregarded. However, when the movement pattern for the PLM test was chosen, the more complex movement pattern of bending down, picking up an object, and transporting it to a stand (Posturo-Locomotor-Manual) had a better discriminatory ability than the isolated movements of walking (L), lifting (M), and rising up (P) or the intermediate complex movements of rising up and walking (PL) and rising up and lifting the object (PM) Hence, the M variable adds complexity to the PLM movement pattern [25].

5.2.1 Conclusions

There were fair to good correlations between several constructed UPDRS III subdomains and the corresponding PLM variables when evaluating data from the full data set. When evaluating the separate diagnostic groups, a fair correlation was found between total UPDRS III and MT for PD in ON and OFF state, but not for MSA and PSP. No or very low correlation was seen between the M variable and the hand/arm subdomain in UPDRS.

5.3 Coherence and variability

Study II evaluated the coherence between the results obtained in an acute L-DOPA challenge measured with the PLM test and with UPDRS III. The majority of PD patients responded positively to a test dose of L-DOPA as measured with either method. Because a clinically relevant improvement is the most appropriate reason for introducing or continuing treatment, we argue that a 6-point cut-off is preferable. In Study II the 6-point cut-off identified more L-DOPA responders than a 10-point cut-off, a 30% improvement, and a 50% improvement and the 6-point cut-off also had the best overlap with the PLM method (Table 2). A decrease of 6 or more points in UPDRS III classified 40/47 of the PD patients as responders, compared to 34/47 with the PLM method; the concordance between the two test methods was 70%. Few of the MSA patients showed improvement after medication with either method (UPDRS 4/17, PLM 3/17); here, the concordance between the two methods was 59%. In the small sample of PSP patients, about 20% responded positively to L-DOPA (UPDRS 2/9, PLM 2/9), with a concordance of 78% between the methods (Table 11).

Table 11. *L-DOPA responses with the two measuring tools*

UPDRS	PD (n=47)				MSA (n=17)				PSP (n=9)			
cut- off	≥6p	≥10p	≥30%	≥50%	≥6p	≥10p	≥30%	≥50%	≥6p	≥10p	≥30%	≥50%
+ in PLM	34	34	34	34	3	3	3	3	2	2	2	2
- in PLM	13	13	13	13	14	14	14	14	7	7	7	7
+ in UPDRS	40	35	34	28	4	0	1	0	2	0	0	0
- in UPDRS	7	12	13	19	13	17	16	17	7	9	9	9
Concordant +	64%	57%	55%	47%	0%	0%	0%	0%	11%	0%	0%	0%
Concordant -	6%	11%	11%	15%	59%	82%	76%	82%	67%	78%	78%	78%
Discordant	30%	32%	34%	38%	41%	18%	24%	18%	22%	22%	22%	22%

Because the PLM test covers a smaller subset of L-DOPA responsive features, the somewhat lower ratio of L-DOPA responders revealed by the PLM method in our material was expected. However, it was also evident that the group of patients who were L-DOPA responsive with UPDRS III, but not PLM, displayed significantly larger variability in both MT_{OFF} and MT_{ON} (SD was 339% of the L-DOPA induced change). Conversely, patients who were positive only with the PLM test had a significantly lower variability in MT_{ON} (29% variability of the L-DOPA induced change). Patients who were congruent in both tests showed a low variability (70% variability of the

L-DOPA induced change) both in OFF and ON (one way ANOVA of logarithmized values; $F(2,51)=12.5$; $p<0.0001$)(Fig. 11) A post hoc t-test revealed significant differences between PLM negative/UPDRS positive patients and the other two groups (figure 11). This was an unexpected but interesting finding, indicating that the PLM method has the ability to detect variability in motor performances both OFF and ON medication and that the variability differs between patients; some patients have a large variability in OFF, others have a large variability in both OFF and ON, and yet others have a very small variability after administration of L-DOPA as compared to before administration of L-DOPA.

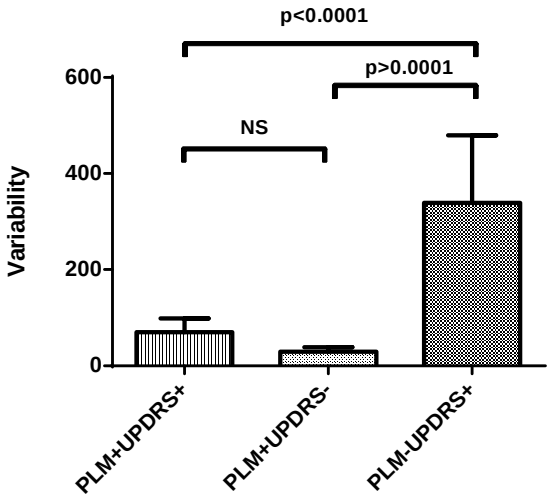

Figure 11. Variability in the group with PLM negative / UPDRS positive patients and the other two groups.

To achieve a positive L-DOPA test, the confidence interval for MT_{OFF} ($MT_{OFF} \pm 1.96$ SD) must be numerically higher and disjoint from the confidence interval for MT_{ON} ($MT_{ON} \pm 1.96$ SD), which might be harder to obtain with a large variation. This might be part of the explanation for the lower sensitivity of the PLM test compared to the UPDRS III. The measured variability in PLM performance raises the question of the best timing of the assessment after an L-DOPA dose.

A study by Colosimo et al. [94] indicated that onset of L-DOPA response might peak differently depending on disease stage. Another study described a short-lived (up to 20 minutes) deterioration of motor symptoms, before improvement occurred, shortly after L-DOPA intake in PD patients on long-term L-DOPA therapy [98]. In fact, any measurement method that does not continuously evaluate L-DOPA response runs the risk of measuring the patient before the L-DOPA takes effect, or missing the best ON value if the measurements take place too long after the intake of medication. In this aspect, the PLM test has an advantage over UPDRS III, where repeated measurements are time consuming and need expertise. In Study II, the UPDRS III ratings were on average performed within the time span of optimal PLM performance (63 ± 25 minutes after L-DOPA administration), and the results from this study indicate that if only one assessment is made, the appropriate time to test L-DOPA response is approximately one hour after L-DOPA administration.

5.3.1 Conclusions

There was a 70 % coherence in the L-DOPA response between the two assessments tools. The PLM method provides repeated measures, with the ability to measure variability in motor performance ON and OFF medication.

5.4 Reliability and discrimination between healthy controls and patients with Parkinsonism

5.4.1 Is the PLM test a reliable method?

The PLM test demonstrated excellent test re-test reliability between tests 1 and 2 in healthy controls [99] (Table 12, Fig. 12).

Table 12. *Intraclass correlation coefficient (ICC) between tests 1 and 2 for healthy controls.*

	Mean	95% CI	ICC	p-value
MT	0.035	-0.199-0.269	0.85	0.0822
P	-0.001	-0.117-0.114	0.85	0.8900
L	0.012	-0.190-0.166	0.87	0.4308
M	0.010	-0.164-0.185	0.85	0.4879
SI	-0.044	-0.241-0.152	0.65	0.0108

There was however a slight systematic increase of 0.04 in SI, indicating an increase in simultaneity in the second test. The ideal situation would be to have stable performances over time, but changes in performance during repeated testing of motor functions are commonly observed; these are often due to adaptive learning processes [100, 101].

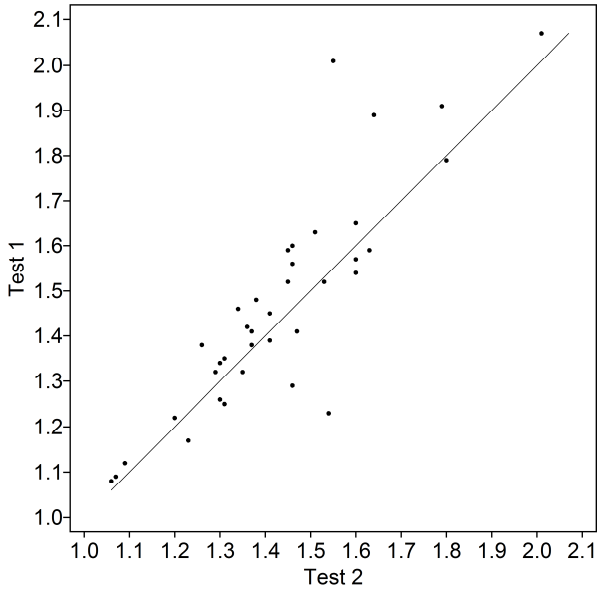

Figure 12. Correlation between MT_1 and MT_2 in healthy controls.

The group of healthy controls was not a good match to the population in terms of gender, but that did not influence the results; the linear regression analysis showed no significant effect of gender on performance. The analysis did however show, as expected, an increase in MT of 0.012 ± 0.004s ($p=0.0046$) per year of age (Fig. 13). This result confirms previous findings using the PLM test, which have found MT to increase with age and to show no significant effects of gender [102].

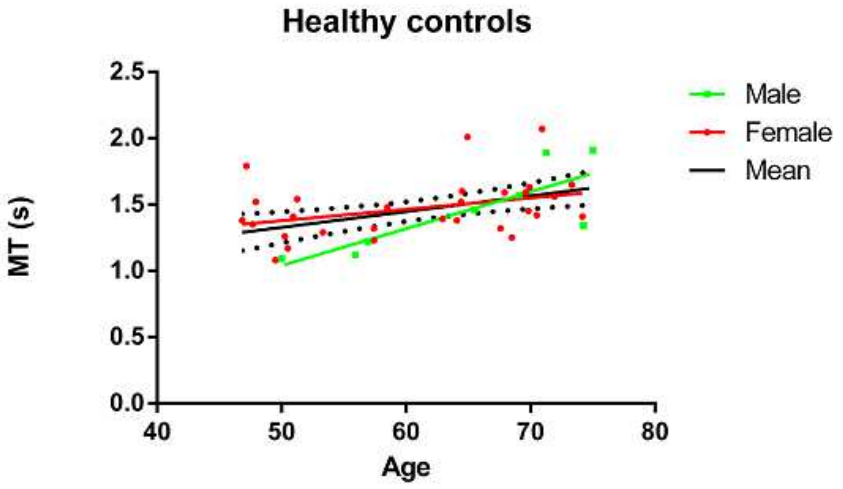

Figure 13. Linear regression analysis for male and female healthy controls.

5.4.2 Can the PLM test distinguish between healthy controls and patients with Parkinsonism?

In study III all of our PLM variables MT_1, P_1, L_1, M_1, SI_1, MT_{OFF}, P_{OFF}, L_{OFF}, M_{OFF}, and SI_{OFF} differed significantly between healthy controls and patients with Parkinsonism off medication, with $p<0.0001$ in all cases. Figure 14 show mean values for the compared PLM vaibles in healthy controls, PD, MSA and PSP patients. Gender differed significantly between healthy controls and patients with Parkinsonism ($p=<0.0001$).

The first PLM measurement in the healthy population was compared to the pre L-DOPA values of the patients. No L-DOPA was administered to the healthy controls, thus making the chosen approach most appropriate. There is conflicting information on the effect of L-DOPA in healthy individuals. Newman et al. [103] found no effects on motor function measured with the Modified Columbia Rating Scale after L-DOPA administration, whereas Floel et al. [104] reported results suggesting that the administration of L-DOPA can improve the fine distal hand movement in healthy elderly people. The best control group would indisputably have been healthy controls undergoing a L-DOPA challenge, but we considered it a safe and rational experimental paradigm to refrain from exposing healthy controls to L-DOPA.

To further analyze the ability of the PLM method to discriminate between healthy controls and patients with Parkinsonism, we performed a logistic regression analysis. Since gender differed significantly between the two groups, it was included as an independent factor to adjust for the demographic differences in the logistic regression analysis.

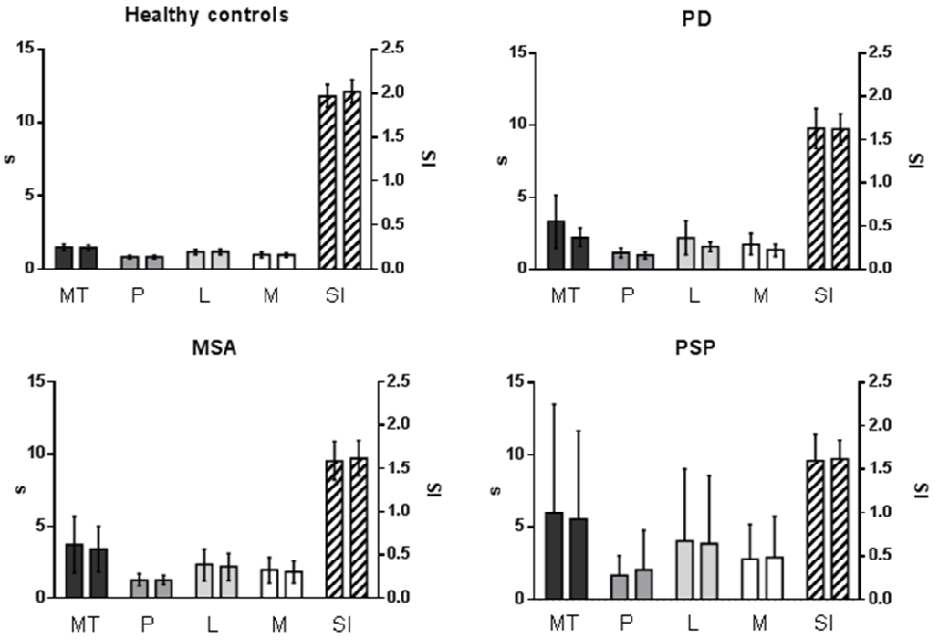

Figure 14. Show the mean values for the compared PLM variable. For the healthy group first column represents first test occasion and the second column the second test occasion 90 minutes apart. For the patients' groups first column represent values in unmedicated state and the second column medicated state

A ROC curve is an aid to visualizing and understanding the trade-off between high sensitivity and high specificity, and is a useful way to evaluate the performance of a diagnostic test aimed at classifying individuals into two categories; in this case, healthy persons and patients with Parkinsonism, patients with PD and patients with atypical PD, and patients with MSA and those with PSP [48]. In the ROC curve, sensitivity and specificity are given for every measuring point and the cut-off value could be determined depending on which is most important: high sensitivity, high specificity, or equally-high sensitivity and specificity. However, the choice of the "best"

cut-off value is not simple. If the cut-off is set too high, one may miss some individuals with low test values or mild forms of the disease (low sensitivity). Few of the positive tests would be wrong, but many of those with a negative test result could in fact be affected by the disease. A low cut-off would capture most of the individuals with the disease, but also persons not affected would be classified as having the disease. The specificity of the test would be low. The AUC is calculated from the ROC curve and is a measure of how well the model discriminates between the two groups.

The linear combination that best differentiated between healthy persons and patients with Parkinsonism was (a + b*(gender) + c*(MT), where MT is MT_1 or MT_{OFF}. Estimates of the beta coefficients a, b, and c that produce the linear combination resulting in the highest AUC are given in Table 13.

Table 13. *Beta coefficients for the linear combination with the highest AUC (healthy controls vs. patients with Parkinsonism).*

Estimates of beta coefficients	Healthy controls vs. patients
Intercept (a)	-9.33 ± 2.98, p= 0.0017
Gender (b)	-2.16 ± 0.87, p= 0.0132
MT_{OFF} (c)	7.14 ± 1.57, p= <0.0001

Beta coefficient ± SD, p-value, male gender =1, female gender =2

The logistic regression analysis indicated that the PLM test strongly discriminates between healthy controls and patients with Parkinsonism using any of the individual PLM parameters (MT, P, L, M, SI). The corresponding AUCs ranged from 0.94 to 0.99, with p-values <0.0001 in each case. The best discriminating variable was MT, producing an AUC of 0.99 (p<0.0001) (Fig. 15).

5.4.3 Conclusions

The PLM test is a reliable method with a high test-retest correlation and a high ability to discriminate between healthy controls and patients with Parkinsonism.

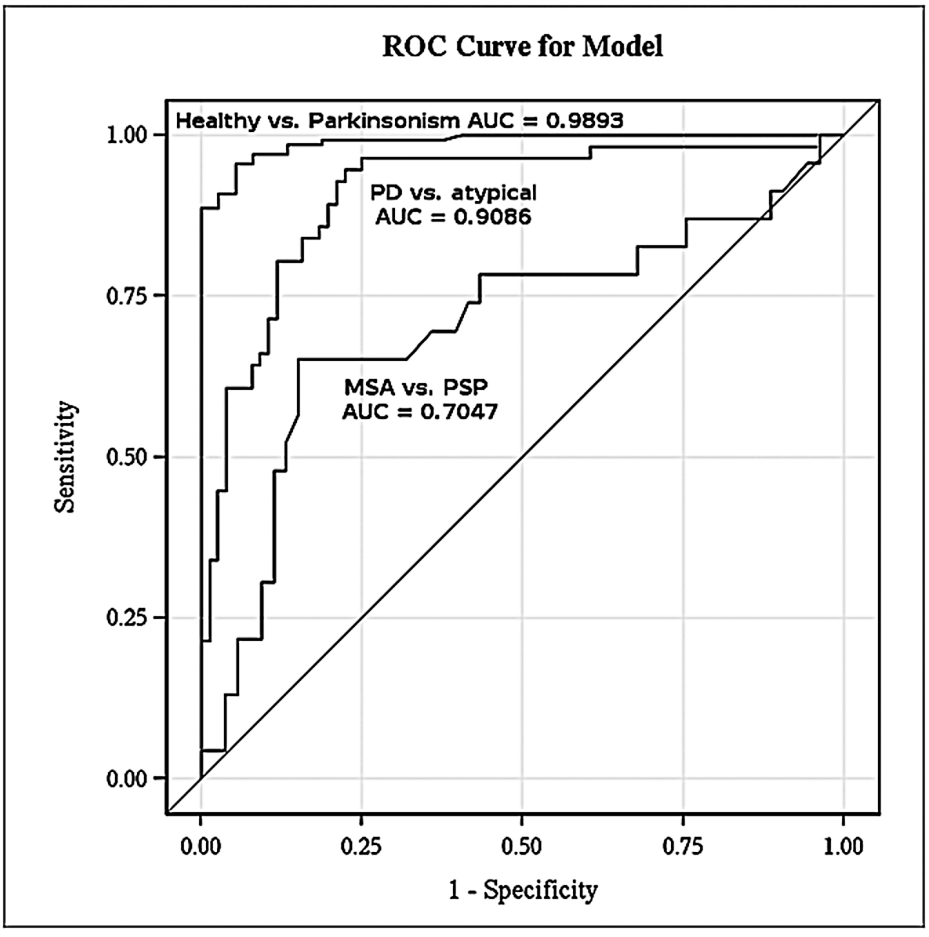

Figure 15. ROC and AUC for discriminating between healthy controls and patients with Parkinsonism; between patients with PD and those with atypical Parkinsonism; and between patients with MSA and those with PSP.

5.5 Discrimination between patients with PD, MSA, and PSP

In study II most of the PD patients showed a significant improvement following acute L-DOPA treatment, measured with both UPDRS III and the PLM method. No such improvement was seen in the MSA and PSP groups (Fig. 16).

The effect of L-DOPA treatment was evaluated with UPDRS III in the diagnostic groups by repeated measure two-way ANOVA. There was a significant interaction between diagnosis and treatment state ($F(2,70)=17.5$, $p<0.0001$) and a significant main effect of treatment state ($F(1,70)=24.2$, $p<0.001$). These effects were explained by a reduction in UPDRS III in PD patients in ON (Fig. 16).

The effect of L-DOPA treatment was also evaluated with the PLM method by repeated measure two-way ANOVA using diagnostic group and treatment state as independent factors. There was a significant main effect of treatment state ($F(1,70)=5.2$, $p=0.0258$) and of diagnosis ($F(2,70)=7.1$, $p=0.0016$). Post hoc analysis revealed that PSP patients had longer MT than the other patient groups in both ON and OFF, and that MT decreased in PD patients but not in MSA or PSP patients after L-DOPA (Fig. 16).

This shows that in this population (Study II), the PLM test could distinguish between the three diagnostic groups on a group level, and the PLM test offers a way to test L-DOPA responsiveness in patients with Parkinsonism of moderately advanced stage.

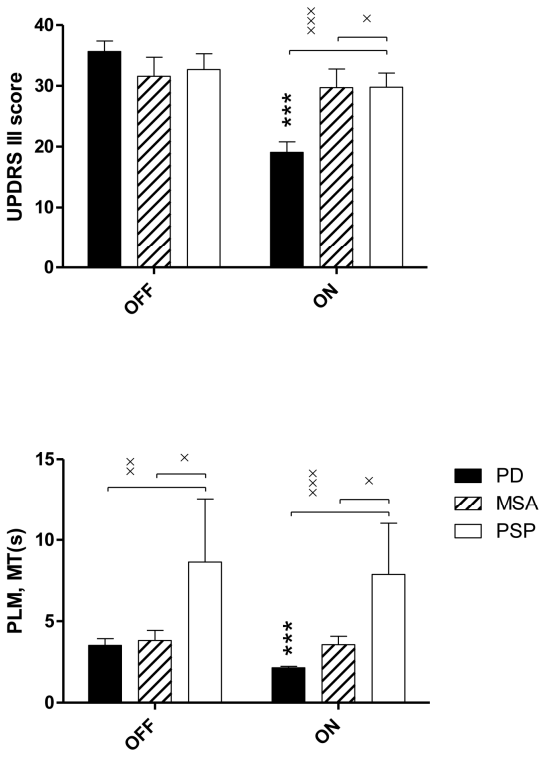

*Figure 16. Panel A: UPDRS III scores before (OFF) and after (ON) 200 mg L-DOPA, stratified over the three diagnoses: Parkinson's disease (PD), multiple system atrophy (MSA), and progressive supranuclear palsy (PSP). Panel B: PLM mean movement time, MT(s), duration. Main effects of diagnosis and treatment state were analyzed with repeated measure two-way ANOVA followed by Bonferroni-corrected t-tests where *** $p<0.001$, PD OFF vs. PD ON, × $p<0.05$, ×× $p<0.01$.*

To further study the discriminatory ability of the PLM method on an individual level, we investigated which PLM variables or combination of variables in retrospect offered the highest discriminatory ability between patients with PD and atypical Parkinsonism (Study III). We also looked at whether the PLM method offers discriminatory properties to distinguish between MSA and PSP.

All PLM variables except SI_{OFF} were significantly different in patients with atypical Parkinsonism compared to PD patients, and the p-values were generally lower for measurements obtained after L-DOPA administration.

This illustrates the L-DOPA response found in the PD group; an increased difference between PD and atypical Parkinsonism ON medication.

In the logistic regression analysis, the individual PLM variables OFF medication displayed lower discriminatory properties, resulting in AUC values around 0.6. This can be compared to the discriminatory properties of variables after L-DOPA administration, which produced AUC values around 0.8.

To investigate if any combination of PLM variable offers an improved discriminatory ability (increased AUC), variables were combined in a forward stepwise multiple logistic regression analysis. The best combination of variables was the relative improvement in MT after L-DOPA ($[MT_{OFF} - MT_{ON}]/MT_{OFF}$) combined with the absolute MT after medication (MT_{ON}). The AUC using this combination was 0.91 (p=<0.0001)(Fig. 15).

The linear combination for discriminating between PD patients and atypical Parkinsonism is given by ($a + d*(MT_{OFF} - MT_{ON}/MT_{OFF}) + e*MT_{ON}$). Estimates of the beta coefficients a, d, and e that produce the linear combination yielding the highest AUC are given in Table 14.

Table 14. *Beta coefficients for the linear combination with the highest AUC (patients with PD vs. patients with atypical PD).*

Estimates of beta coefficients	PD vs. atypical PD	p-value
Intercept (a)	2.42 ± 0.81	0.003
$(MT_{OFF} - MT_{ON})/MT_{OFF}$ (d)	0.07 ± 0.02	<0.0001
MT_{ON} (e)	-1.38 ± 0.32	<0.0001

The fact that the PLM test has the capacity to accurately discriminate between healthy controls and patients with Parkinsonism is interesting; however, this is only what is expected from any useful laboratory method in this situation. It is more interesting that the PLM test had a good discriminatory ability for distinguishing PD patients from patients with atypical Parkinsonism. This is a less straightforward task, and some 20% of patients with Parkinsonism in a general practice setting are incorrectly diagnosed [67]. Trained movement disorder specialists can have a diagnostic accuracy of over 95% [67] in relation to histopathological findings. We do not know the histopathological diagnoses in the current study, and with an AUC of 0.91, the PLM test may be less accurate than assessment by a movement disorder specialist.

Previously in a smaller study, the ability of the PLM test in combination with analysis of levels of the neurofilament in cerebral spinal fluid (CSF-NFL) was used to differentiate between PD, MSA, and PSP. The PLM test correctly classified 85% of the patients, with a sensitivity of 84% and a specificity of 86% to recognize atypical PD. This discriminatory ability increased when the results from the PLM test and CSF-NFL were combined; 95% of patients were then correctly classified, with a sensitivity of 94% and a specificity of 88% for atypical PD [105].

Combinations of behavioral measures and neuroimaging have also shown potential to increase the ability to differentiate between patients with Parkinsonism. In a study by Busse et al. [106], assessment of midbrain hyperechogenicity could discriminate between PD and atypical PD with a specificity of 63%, and when assessment of motor asymmetry and hyposmia was added, the specificity increased to 98%. Neely et al. [107] combined a cognitive test with analysis of pulsed grip forces and increased the specificity to discriminate between PD and PSP from 91.7% to 100%.

One important fact is that most discriminatory studies are performed in patients with a clear-cut diagnosis [105, 106, 108]. However, the observed diagnostic accuracy of the PLM test is high enough to be of clinical relevance [109, 110], and the test can be administered and interpreted by less-trained professionals.

The patients considered most difficult to diagnose clinically are those with MSA-P. Using two cut-off values (Fig. 17), a lower one with high specificity for atypical Parkinsonism and a higher one with high specificity for PD the PLM method had the ability to classify 98/132 patients with a specificity of 94.6% and a sensitivity of 76.3% for atypical Parkinsonism if $(a + d*(MT_{OFF} - MT_{ON}/MT_{OFF}) + e*(MT_{ON}) < -0.765$ and a specificity of 96.1% and a sensitivity of 60.7% for PD if $(a + d*(MT_{OFF} - MT_{ON}/MT_{OFF}) + e*(MT_{ON}) > 0.751$. Of the 34 unclassified individuals, 13 had MSA (11 MSA-P, 2 MSA-C), 2 had PSP, and 19 had PD.

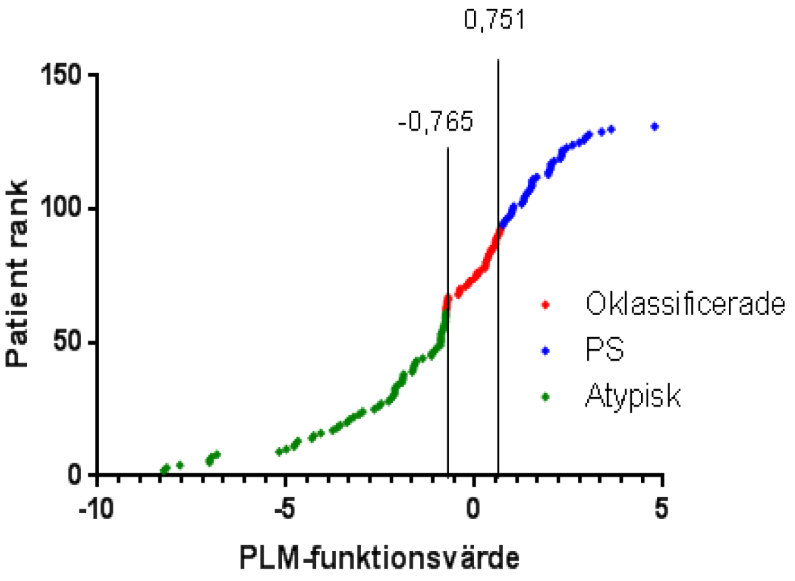

Figure 17. The use of two cut-off values: a lower value with high specificity (94.6%) for atypical Parkinsonism (< -0.765) and a higher value with high specificity (96.1%) for PD (> 0.751). Values for two patients with atypical Parkinsonism were omitted from the graph due to very high PLM function values (-39 and -19).

In terms of the PLM method's capacity to discriminate between MSA and PSP, only M_{ON} had a significant (but moderate) accuracy in discriminating between the two diagnostic groups (AUC=0.71, p=0.018, Fig. 15). In patients with atypical Parkinsonism, the linear combination for discriminating between MSA and PSP patients using the PLM variable M_{ON} was ($a + f * M_{ON}$), with values of the beta coefficients as follows: $a = -2.5 \pm 0.75$ (p=0.0008) and $f = 0.79 \pm 0.33$ (p=0.0175).

5.5.1 Conclusions

Study II showed that the PLM variable MT could significantly differentiate on a group level between the patient groups of PD, MSA, and PSP due to the positive L-DOPA response in the PD group and a significantly longer MT in the PSP group OFF and ON medication. This could not be confirmed on an

individual level (Study III), but we did show that the PLM test had a highly accurate discriminatory ability to separate between patients with PD and patients with Parkinsonism but the test could not differentiate between MSA and PSP.

5.6 The PLM method as an assessment tool in early-stage Parkinson's disease

In Study IV, the effect of high frequency rTMS applied over the motor cortex was evaluated with UPDRS III and the PLM method. A significant decrease in total UPDRS III was found contralateral to the stimulated side after two sessions of rTMS and the patient's ordinary morning medication (Fig. 18).

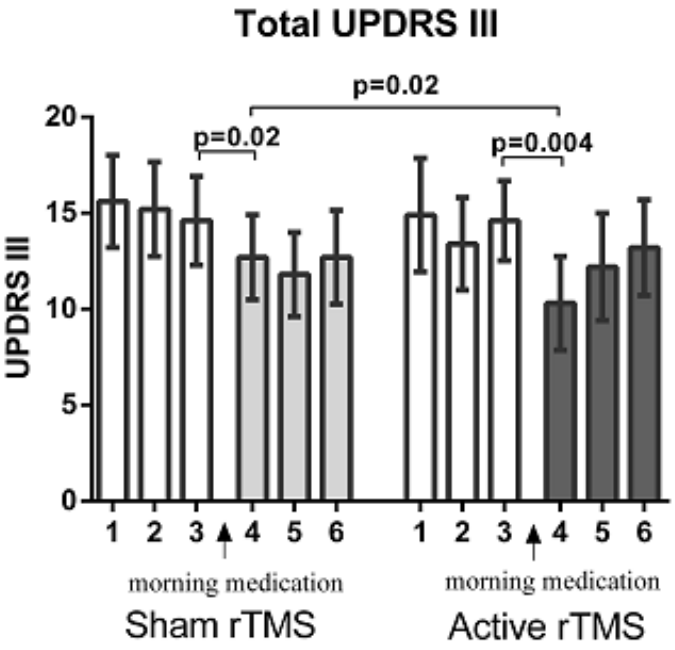

Figure 18. Total UPDRS III scores for all evaluation sessions. Filled bars indicate total UPDRS III scores after administration of the patient's ordinary morning medication.

The main part of the improvement in the total scores after active/sham rTMS and medication was found in the bilateral hand/arm UPDRS III items (active group decrease of 3.3 ± 0.6 vs. sham group decrease of 1.3 ± 0.6; p=0.03) and

further analysis of the hand/arm scoring revealed that there was a significant decrease in scores on the most affected side, the stimulated side (p=0.002).

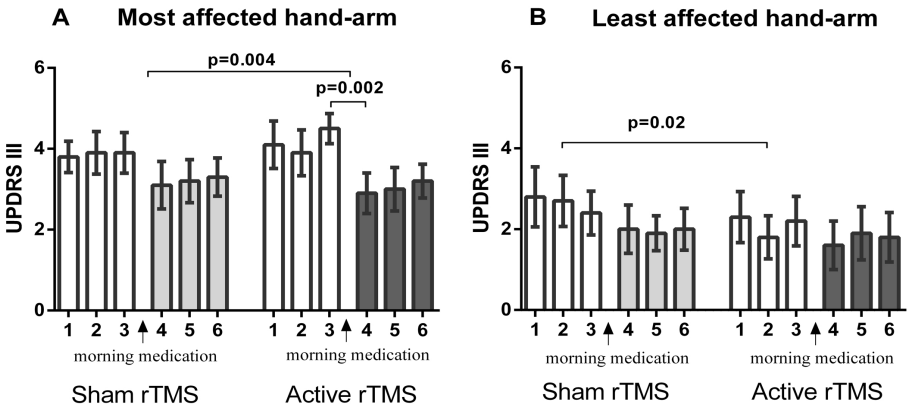

Figure 19. Improvements in hand/arm related UPDRS III scores on the worst side and best side. Filled bars indicate UPDRS III hand/arm scores after administration of the patient's ordinary morning medication.

No significant decrease was seen in the sham group after medication (active group decrease of 2.3 ± 1.1 vs. sham group decrease of 0.7 ± 1.5; p=0.004, Fig. 19A). There was a significant larger decrease in UPDRS III scores on the better side after the first active rTMS compared to sham stimulation (UPDRS 2 active vs. UPDRS 2 sham p=0.02, Fig. 19B). No significant decrease in UPDRS hand/arm scores was detected after medication on the least affected side (Fig. 19), No significant effect of either sham rTMS or active rTMS was seen in the UPDRS III subscores for leg or other items (for details on UPDRS III subscores, see section 3.4.2).

The PLM method could not detect any significant effects of either sham rTMS or active rTMS in any of the PLM variables (MT, P, L, M or SI) (figure 20). Only one patient showed a positive response to the anti-parkinsonian medication in the sham group, and one other patient showed a positive response in the active group as measured with the PLM method (for details on a positive response, see section 3.5.1).

The symptoms of most of the patients in the study group were dominated by upper-limb symptoms, as illustrated in a larger proportion of scores from the hand/arm related UPDRS III items (Fig. 19). The largest improvement in UPDRS III after medication also occurred in the hand/arm related items. This may explain why the PLM method did not detect a change in performance, as

the strongest correlation between PLM and UPDRS III was in gait and posture related items, and there was no significant correlation between the manual phase of the PLM test and the UPDRS III hand/arm items [111].

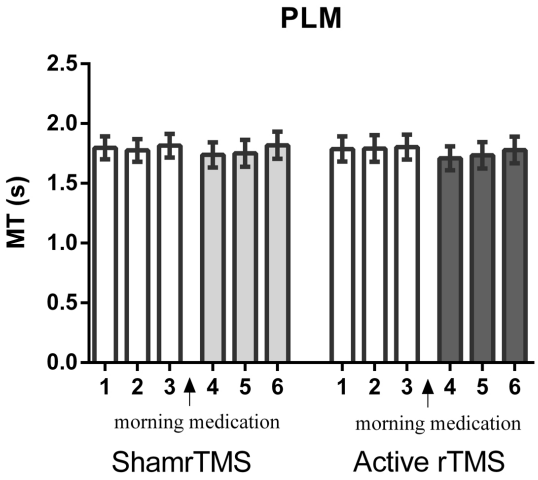

Figure 20. A PLM test was performed after each UPDRS evaluation of the patients. The bars show movement times (MT) in seconds for sham rTMS and active rTMS at the six different measuring points. Filled bars indicate MT after administration of the patient's ordinary morning medication.

UPDRS III was able to detect medication response in terms of significant improvement in total UPDRS III; however, in the sham session, none of the patients showed the 6-point improvement that has been suggested as being clinically important [73, 112]. In the active rTMS session, only three patients improved by 6 points or more after medication and rTMS stimulation.

The poor detection of the medication response in PLM performance might be explained by the patients' mild symptomatology, and to some extent by the fact that the OFF condition was relatively prolonged (morning medication was administered at 11.15am-11.30am), which might have led to a decreased "best possible" ON effect.

Nevertheless, the rTMS study illustrates an important limitation in the usefulness of the PLM test. It is clear that the test has poor sensitivity to mild to moderate symptoms which mainly affect hand and arm function. Study II, which showed a fair to good correlation between most UPDRS III subdomains and the PLM phases (the only exception being the hand/arm domain and the M phase), was performed in patients at more advanced stages

of the disease, with most of the measurements made during the workup for deep brain stimulation surgery. The results of Study IV, showing a low sensitivity of the PLM test to symptoms in early PD patients and are, are in line with previous results [113].

5.6.1 Conclusions

The PLM method did not have the ability to detect improvement in motor function in early-stage PD patients with symptoms predominantly from the upper extremities.

5.7 Limitations

All patients were diagnosed following strict diagnostic criteria. We had no neuropathological confirmation of the clinical diagnosis, and cannot rule out the possibility that some of the patients might have been misdiagnosed; however, in all studies except for Study IV the study population had had a relatively long disease duration, and had passed the early stages when correct diagnosis is more difficult. Multiple tests may have introduced Type 1 errors. The findings are nevertheless in line with the general view of what factors best differentiate between PD and atypical Parkinsonism [114]. The studies did not have enough power for a reliable conclusion regarding the usefulness of the PLM test for discriminating between different diagnoses in patients with atypical Parkinsonism (MSA, PSP), which largely reflects the reality of low incidence and prevalence of atypical Parkinsonism. For half of the patients in Study IV, the morning L-DOPA dose was lower or much lower than the usual 200 mg test dose, which may explain the poor response after a prolonged abstinence from medication.

6 CONCLUSIONS

Taken together, the findings presented in this thesis suggest that the automated implementation of the PLM test (QbTestMotus) generates data that are consistent with the measurements made by the previous semi-automated method. The PLM method is a reliable and objective instrument for measuring motor function in ambulatory patients with Parkinsonism and may be a useful method to objectively assess motor impairments and medication response in patients with moderately advanced Parkinson's disease. The PLM can potentially aid the diagnostic process of differentiating between PD and atypical Parkinsonism in moderate to advanced disease. However, it cannot reliably detect acute treatment response in early-stage Parkinson's disease with symptoms predominantly from the upper limbs, and use of the PLM test for diagnostic purposes at other disease stages than moderate to advanced disease cannot be recommended.

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APPENDIX

Hoehn and Yahr staging of Parkinson's disease

1. Stage One
    1. Signs and symptoms on one side only
    2. Symptoms mild
    3. Symptoms inconvenient but not disabling
    4. Usually presents with tremor of one limb
    5. Friends have noticed changes in posture, locomotion, and facial expression
2. Stage Two
    1. Symptoms are bilateral
    2. Minimal disability
    3. Posture and gait affected
3. Stage Three
    1. Significant slowing of body movements
    2. Early impairment of equilibrium on walking or standing
    3. Generalized dysfunction that is moderately severe
4. Stage Four
    1. Severe symptoms
    2. Can still walk to a limited extent
    3. Rigidity and bradykinesia
    4. No longer able to live alone
    5. Tremor may be less than earlier stages
5. Stage Five
    1. Cachectic stage
    2. Invalidism complete
    3. Cannot stand or walk
    4. Requires constant nursing care

MODIFIED HOEHN AND YAHR STAGING

STAGE 0 = No signs of disease
STAGE 1 = Unilateral disease
STAGE 1.5 = Unilateral plus axial involvement
STAGE 2 = Bilateral disease, without impairment of balance
STAGE 2.5 = Mild bilateral disease, with recovery on pull test
STAGE 3 = Mild to moderate bilateral disease; some postural instability; physically independent
STAGE 4 = Severe disability; still able to walk or stand unassisted
STAGE 5 = Wheelchair bound or bedridden unless aided

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