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Graphical tasks to aid in diagnosing and monitoring Parkinson's disease

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CHAPTER 1

GENERAL INTRODUCTION

1.1. Parkinson's disease

Parkinson's disease (PD) was first described in 1817 by James Parkinson. There is ample knowledge regarding the symptoms and characteristics of PD, but the cause of PD is still largely unknown. PD is a neurodegenerative disorder that is often characterized by motor symptoms. The four cardinal motor symptoms are bradykinesia (slow movement), resting tremor (trembling of a body part in rest), rigidity (muscular stiffness), and balance problems^[1]. In addition, other motor symptoms can be observed, such as freezing, shuffling gait, hypomimia (loss of facial expression) and micrographia (reduction in size of handwriting)^[2]. PD has a prevalence of approximately 1.8 per 1000 in the European population and is primarily a disease of the elderly and middle-aged, but can occur in all age groups^[3]. The average age at onset is 60 years. PD is a chronic and progressive disease and current treatment options are symptomatic. Unfortunately, signs of PD can be misdiagnosed by ascribing the signs of disability to normal aging or other movement disorders^[4-6]. Current clinical diagnostic strategies are mainly based on the physician performing an assessment of motor and non-motor symptoms. Diagnostic accuracy clearly improves with increasing clinical experience^[2,4,7]. As patients not always have access to movement disorders specialists diagnosis can be delayed. Yet, early diagnosis is important, as it allows early intervention and management toward an improved overall outcome for the patient^[8].

1.2. Clinical assessment of Parkinson's disease

According to diagnostic criteria, developed by the UK Parkinson's Disease Society Brain Bank, probable PD can be diagnosed when bradykinesia and one other cardinal motor symptom are present^[2]. PD is a clinical diagnosis and the accuracy and reliability of assessing motor symptoms depend on the experience and interpretation of a clinician^[2,9]. The most widely used clinical method to assess motor symptoms of PD is the motor part (part III) of the Unified Parkinson's Disease Rating Scale (UPDRS-III)^[10] or the Movement Disorder Society (MDS)-sponsored revision (MDS-UPDRS-III)^[11]. However, the UPDRS-III has several limitations. Firstly, the UPDRS-III has limited sensitivity in mild stages of the disease and subtle motor signs could easily be missed^[12]. Secondly, the inter-rater reliability is high for movement disorder specialists, but unfortunately not all patients have access to specialized movement disorder centres^[13,14], which negatively influences the accuracy and reliability of the

UPDRS-III. Thirdly, the UPDRS-III needs to be evaluated by a trained assessor, which makes it less suitable for home-based monitoring. To add, when the UPDRS-III is used as monitoring tool, UPDRS scores between regular visits to a neurologists are compared^[15]. However, PD patients are often seen by different clinicians during their regular visits, making comparison of UPDRS scores between visits less reliable. To potentially overcome these limitations and to aid in the assessment of Parkinsonian symptoms, quantitative assessment of these symptoms would be useful.

1.3. Quantitative assessment of Parkinson's disease

The overall objective of the work described in this thesis was to design and evaluate quantitative measures to assess motor symptoms of PD. Quantitative assessment of motor symptoms of PD could be used to aid in the diagnostic process, by enabling general practitioners, nurses, or others not specialized in neurology and movement disorders to timely identify potential cases of Parkinsonism. However, such methods cannot replace the clinical evaluation, since diagnosing PD involves more than the assessment of motor symptoms. It includes careful history taking and the assessment of non-motor symptoms^[1]. Therefore, quantitative assessments of motor symptoms of PD could serve as a screening tool or as add-on in the diagnostic process. The first important step to test whether such assessments could be useful in the diagnostic process is to investigate whether test results in PD patients differ from those in HC participants^[16]. Second, it is important to assess the reproducibility of test results, which refers to the ability of a method to obtain the same test result on repeated testing^[17]. Reproducibility tests should initially be performed in HC participants, since performance on the test is not influenced by medication or disease state in this group.

If patients do have timely access to neurologists, quantitative assessment of motor symptoms of PD could be of additional value in the differentiation between PD and other movement disorders. Therefore, the next step would be to test whether quantitative assessment of motor symptoms can be used to discriminate between typical and atypical Parkinsonism and essential tremor (ET). It is thus important to investigate whether test results in PD patients differ from those in patients with other movement disorders (MD^[16]). Furthermore, the diagnostic accuracy of a new method should be determined, which refers to the ability of a method to correctly detect or exclude PD^[17]. This can best be done by comparing results of the new method to the results of a reference standard, such as the UPDRS, in a group of clinically relevant

patients^[17]. Not only the diagnostic process could be improved, but quantitative assessment of motor symptoms of PD could also be used for monitoring treatment effects, by investigating changes in performance after medication intake.

In the next sections of this chapter we will review the existing literature regarding quantitative assessment of motor symptoms of PD (see Table 1.1). The most important findings of previous studies regarding the validation steps described in the previous paragraphs are summarized and discussed. Quantitative assessment of motor symptoms of PD is mostly done by observing upper limb function^[18,19]. In the next sections we focus on the quantitative assessment of the cardinal motor symptoms bradykinesia and tremor in the upper limb. Rigidity, which refers to an increased muscle tone noticed during subjective assessment by a physician during passive movements of, for example, the affected arm^[1], is very hard to quantify. Additionally, we discuss the quantitative assessment of micrographia. Micrographia refers to a reduction in the size of handwriting, is common in PD^[1], and also involves impairment of upper limb function.

1.4. Quantitative assessment of bradykinesia

The term bradykinesia means ‘slow movement’. The term was first used by James Parkinson to describe one of the motor symptoms of PD. During clinical examination bradykinesia of the upper limb is typically assessed by observing the patient perform finger tapping, opening and closing hand movements, and pronation and supination movements of the hand (‘diadochokinesis’). A clinician rates performance on these tasks according to the UPDRS, where a score of 0 is given when performance is normal and a maximum score of 4 is given when the patient is severely impaired on the task. The clinician evaluates speed, amplitude, hesitations, halts and decrementing amplitude for each side separately. Quantification of performance on the UPDRS task ‘finger tapping’^[20-26] and the ‘diadochokinesis’ task^[22,27,28] was studied previously. In these studies movement sensors, such as accelerometers, gyroscopes and magnetometers, were attached to the index finger and/or thumb to investigate the kinematics of the finger tapping movement or to the wrist or back of the hand for the ‘diadochokinesis’ task.

As described previously in this chapter, several important steps should be followed in diagnostic research. Individual studies that described quantitative assessment of the ‘finger tapping’ and ‘diadochokinesis’ task, investigated some, but usually not all of these steps. For example, differences were found between

PD patients and HC participants in speed and amplitude of the finger tapping task^[20,24–26] and in angular velocities during the ‘diadochokinesis’ task^[22,27,28], when assessed by movement sensors. Three studies^[21,22,24] found high correlations between the output of movement sensors and other clinical measures, such as UPDRS scores on the ‘finger tapping’ task^[21,22,24] or the Purdue pegboard test^[21]. Furthermore, high test-retest reliability was found for using movement sensors to quantify the ‘finger tapping’ task^[23]. To show that movement sensors to assess bradykinesia could also be used to monitor treatment effects, Espay et al.^[21] investigated changes in speed and amplitude of the finger tapping task after taking medication in PD patients and showed improvement.

Thus, movement sensors can be used for the quantitative assessment of bradykinesia. However, such methods all involve attaching sensors to the skin, which might be inconvenient for the patient and could be time-consuming. For this reason, other tasks and methods have also been investigated for their ability to provide objective measures of bradykinesia. For example, performance on graphical tasks, such as handwriting and drawing, could provide information on the slowness of movement in PD patients and thus about bradykinesia. The recent introduction of relatively cheap digital tablets enables kinematic analysis of movements during graphical tasks. Recordings of pen-tip movement on a digital tablet, for example, can be used to analyse the duration of and velocity during graphical tasks. Recently, Letanneux et al.^[29] provided an overview of previous studies that investigated graphical tasks employing a digital tablet. Many of the studies that were included in their review, reported measures to assess bradykinesia, such as duration and velocity. Graphical tasks mainly included the writing of a sentence or repeated letter patterns (‘e’ and ‘l’)^[30–35], but some studies also included figure tracing and drawing tasks, involving circles^[30,36], spirals^[37] or lines^[30,38]. Letanneux et al.^[29] reported that only half of these studies found a significant difference between PD patients and HC participants based on the duration of graphical tasks. In contrast, almost 80% of these studies showed significant differences between PD patients and HC participants for velocity measures. The fact that half of the studies found that duration was similar for PD patients and HC participants could be due to the fact that many of these studies included free drawing and writing tasks, where there was no restriction in size of drawing and writing. In such tasks, PD patients might have compensated their slowness by reducing the size of writing and drawing^[29]. Hence, velocity of graphical tasks seems to be a better measure to assess bradykinesia than duration. Or, when investigating duration of graphical tasks, patients should trace or copy figures rather than perform free writing or drawing

tasks. Additionally, Letanneux et al.^[29] reported some studies that investigated differences in performance on graphical tasks between PD patients off and on treatment. The studies that investigated the change in duration (n=7) and velocity (n=4) of graphical tasks after taking medication in PD patients, all showed significant differences between off and on treatment measurements. Thus, duration and velocity are both important measures to take into account, when using graphical tasks to monitor disease progression and treatment effects in PD patients. Finally, Banaszkiwicz et al.^[37] investigated the validity of a spiral drawing task to assess bradykinesia by comparing it to the UPDRS scores and showed a high correlation.

1.5. Quantitative assessment of tremor

Tremor is another cardinal symptoms of PD^[1]. However, not all PD patients suffer from tremor. Often, PD is divided into tremor dominant and non-tremor dominant subtypes^[39]. Tremor dominant PD patients initially present with tremor and relatively mild bradykinesia and rigidity^[40]. Tremor, in general, is defined as a rhythmical, involuntary oscillatory movement of a body part^[41]. Resting tremor is typical for PD and occurs in a body part that is not voluntarily activated and is completely supported against gravity^[41]. Overall, PD and other tremor syndromes can be diagnosed by a specialist based on their clinical presentation^[42], if this clinical presentation is typical. However, in many cases the symptoms are not typical and do not lead to a clear diagnosis, which makes it difficult to find a suitable treatment. For example, ET sometimes shows a continuation into the resting condition, which makes it difficult to distinguish ET from Parkinsonian tremor. For that reason, computerized tremor analysis methods have been proposed to quantify important tremor characteristics in PD patients and in other patients presenting with tremor to aid in the diagnostic process or to monitor disease progression and treatment effects.

Similar to the quantification of bradykinesia, tremor has been quantitatively assessed in PD patients using movement sensors^[28,43-47]. Two studies used a 'tremor pen', which was held by the patient^[43,44]. Salarian et al.^[28] used a gyroscope attached to the forearms, while Muthuraman et al.^[45] used accelerometers attached to the forearms and Wile et al.^[46] used a combination of accelerometers and gyroscopes in a wrist-watch. These studies all included tremor recording during rest and during posture, which involved holding the arms outstretched. The outcome measures included tremor frequency, tremor intensity and tremor amplitude, which were significantly different between PD and ET patients^[44,47] or between PD patients and HC participants^[28,43]. Two

studies reported that mean harmonic peak power could be used to distinguish PD from ET patients^[45,46].

Although these movement sensor-methods provide useful measures to assess tremor, these methods are time-consuming and might be inconvenient for the patient when sensors have to be attached to the skin. Therefore, other methods have also been investigated to assess tremor, such as graphical tasks employing a digital tablet. Spiral drawing, for example, has extensively been investigated to assess tremor^[48-58]. However, some of these studies used a 'spiral severity' score to assess tremor and since scores are provided by raters, this method is not objective^[50,56-58]. Other studies that investigated a spiral drawing task involved the assessment of tremor frequency and amplitude^[48,51,53,54], tremor intensity^[55], tremor magnitude^[52] or mathematical spiral indices^[49,53]. Such methods have been shown to provide features that correlate with other (clinical) measures to assess tremor in PD patients, such as accelerometry^[48] or UPDRS-tremor scores^[53]. Most studies focused on tremor patients (other than PD) and showed, for example, that tremor patients were different from HC participants based on quantitative tremor assessments during a spiral drawing task^[51,52]. Kraus and Hoffman^[54] and Haubenberger et al.^[55] validated the assessment of tremor frequency, amplitude and intensity in groups of tremor patients, by showing correlations with a visual spiral rating method.

Besides the spiral drawing task, other graphical tasks have been investigated to quantitatively assess tremor. For example, the writing of repeated patterns of the letter 'e' and/or 'l'^[48,52] and figure drawing tasks, such as line drawing^[52,59], circle drawing^[52] and triangle drawing^[59,60] have been studied to assess tremor. Elble et al.^[48] showed that tremor frequency and amplitude could be quantitatively assessed during writing of the letters 'e' and 'l' in ET patients and Ulmanova et al.^[52] showed differences in tremor magnitude between ET patients and HC participants during writing of the letter 'l', drawing lines and circles. Accardo et al.^[59] described that several parameters, including tremor frequency, calculated from line and triangle drawing tasks were different between pathological tremor patients and HC participants. In addition, Geny et al.^[60] observed that tremor was less intense during the ascending phase of a triangle drawing task in ET patients.

1.6. Quantitative assessment of micrographia

Holding a pen and performing handwriting is an important skill in daily life, but also one of the most complex fine motor functions of humans^[61]. Neurodegenerative movement disorders, like PD, could cause deterioration in

handwriting ability^[2,62]. Typically, impairments in handwriting in PD patients are characterized as ‘micrographia’^[29,63]. Micrographia refers to a reduction in writing size in general (‘consistent micrographia’) or to a progressive reduction in writing size (‘progressive micrographia’), which is caused by an inability to maintain a certain writing size for more than a few letters or words^[29]. Consistent micrographia is generally assessed by calculating average width, height and/or length of written samples and progressive micrographia is typically assessed by calculating the difference in width, height and/or length between the first and last sample of a writing task. Several approaches have been used to define micrographia. For example, in some studies micrographia was defined as writing size of PD patients being 50% or 2 standard deviations smaller than the average writing size of HC participants^[25,64]. Other studies assessed micrographia by investigating whether writing size was significantly different between PD patients and HC participants^[31,33–35,65,66]. According to a few studies^[25,63,64,66,67], the prevalence of micrographia in cohorts of PD patients varies between 15% and 60%.

Micrographia (both consistent and progressive) can be detected with conventional paper-and-pencil methods, by measuring width, height and/or length of written sentences, words^[68] or letters^[64,66,69] on paper. However, these methods are time consuming and the use of digital tablets allows a much quicker and easier assessment of micrographia^[29]. Consequently, most of the studies, which have been performed during the last 10–20 years, used a digital tablet to record and analyse graphical tasks^[29]. The assessment of micrographia was often based on the analysis of a repetitive pattern of the letter ‘l’^[30,34,70–75], or the analysis of a sentence writing task, which included words containing the (repetitive patterns of the) letters ‘l’ and ‘e’^[31,33,65,76–80]. The analysis was typically based on stroke size, by separating the data in up- and downward strokes of which the width and/or height was calculated^[30,31,33,34,65,70–80]. Additionally, two studies investigated sentence length^[65,68] and one study investigated the size of the letter ‘a’^[25].

To examine whether the assessment of micrographia might be useful in the diagnostic process of PD, several studies investigated the differences in writing size between PD patients and HC participants. According to Letanneux et al.^[29] 58% of these studies found significant differences between PD patients and HC participants. To our knowledge, no studies investigated test-retest reliability of micrographia assessments and only one study compared writing size between PD patients and patients with other MD and showed that micrographia was more present in PD patients than in patients with other MD^[69]. One study reported that micrographia, defined by a 50% smaller writing size than the average writing

size of HC participants, was more common in progressive supranuclear palsy (PSP) (75%) than in PD patients (15%), which is probably due to the fact that PSP patients are more severely impaired compared to PD patients. To investigate whether micrographia assessments are useful to monitor disease progression and treatment effects, differences in writing size between PD patients off and on medication were studied. Letanneux et al.^[29] reported that 50% of these studies found significant changes in writing size after taking medication in PD patients. Only one study investigated the correlation between the UPDRS motor score and micrographia assessments^[64]. They investigated consistent micrographia and progressive micrographia separately, and found no significant correlation between the UPDRS and consistent micrographia. They did find a weak, but significant correlation between the UPDRS and progressive micrographia. To add, Ondo and Satija^[68] showed that micrographia significantly improved when performing a writing task with eyes closed compared to performing the task with eyes open and Ma et al.^[81] showed that progressive micrographia was present in horizontal writing but not in vertical writing.

Table 1.1. Reviewed literature on studies regarding quantitative assessment of movement disorder symptoms.*

Author	Year	Measurement system	Tasks	Outcome measures related to:		
				Bradykinesia	Tremor	Micrographia
Sensor systems						
Farkas et al. ^[43]	2006	Tremor pen CATSYS	Resting		x	
Salarian et al. ^[28]	2007	Gyroscopes	Posture	x	x	
Koop et al. ^[27]	2008	Gyroscopes	Finger tapping and Diadochokinesis	x		
Shima et al. ^[26]	2008	magnetic sensors	Finger tapping	x		
Espay et al. ^[21]	2009	Electromagnetic sensors	Finger tapping	x		
Papapetropoulos et al. ^[44]	2010	Tremor pen CATSYS	Resting and Posture		x	
Heldman et al. ^[22]	2011	Kinesia	Hand movements UPDRS	x		
Kim et al. ^[24]	2011	Gyrosensor	Finger tapping	x		
Muthuraman et al. ^[45]	2011	Accelerometry	Posture		x	
Ling et al. ^[25]	2012	Infrared-emitting diodes	Finger tapping	x		x
Lacy et al. ^[20]	2013	Electromagnetic sensors	Finger tapping	x		
Bhidayasiri et al. ^[47]	2014	Accelerometry & Gyroscopes	Resting and Posture		x	
Heldman et al. ^[23]	2014	Kinesia	Finger tapping and Tremor tasks UPDRS	x		
Wile et al. ^[46]	2014	Accelerometry	Resting and Posture		x	
Graphical tasks						
McLennan et al. ^[63]	1972	Paper & pen	Sentence, signature			x
Teulings and Stelmach ^[76]	1991	Digital	Sentence 'ellehell'			x
Contreras-Vidal et al. ^[67]	1995	Digital	Sentence			x
Eichhorn et al. ^[36]	1996	Digital	Circles	x		
Elble et al. ^[48]	1996	Digital	Spiral, 'l', '---', 'OOO'		x	
Oliveira et al. ^[70]	1997	Digital	'llll'			x
Teulings et al. ^[71]	1997	Digital	lines, circles, 'llll' patterns			x
Contreras-Vidal et al. ^[77]	1998	Digital	Repeated 'le' and 'hell'			x
Poluha et al. ^[32]	1998	Digital	Repeated 'le' and 'hell'	x		
Pullman et al. ^[49]	1998	Digital	Spirals		x	
Van Gemmert et al. ^[78]	1998	Digital	Sentence			x

Siebner et al. ^[79]	1999	Digital	Sentence			x
Van Gemmert et al. ^[30]	1999	Digital	'8', circle, 'llll'	x		x
Van Gemmert et al. ^[72]	2001	Digital	Sentence			x
Contreras-Vidal et al. ^[73]	2002	Digital	'llll'			x
Teulings et al. ^[74]	2002	Digital	'llll'			x
Van Gemmert et al. ^[75]	2003	Digital	'llll' and 'lilili'			x
Kim et al. ^[64]	2005	Digital	Luria loops			x
Ondo et al. ^[50]	2005	Digital	Spiral		x	
Caligiuri et al. ^[80]	2006	Digital	'hellohello'			x
Lange et al. ^[33]	2006	Digital	Sentence	x		x
Miralles et al. ^[51]	2006	Digital	Spiral		x	
Tucha et al. ^[31]	2006	Digital	Sentence	x		x
Ondo and Satija ^[68]	2007	Digital	Sentence			x
Ulmanova et al. ^[52]	2007	Digital	Spiral and 'elel'		x	
Ponsen et al. ^[65]	2008	Digital	Sentence			x
Saunders-Pullman et al. ^[53]	2008	Digital	Spiral		x	
Banaszkiewicz et al. ^[37]	2009	Digital	Spiral	x		
Broderick et al. ^[38]	2009	Digital	'^^^'	x		
Accardo et al. ^[59]	2010	Digital	'---', triangle, square		x	
Kraus and Hoffman et al. ^[54]	2010	Digital	Spiral		x	
Bidet-Ildei et al. ^[34]	2011	Digital	'lll' and 'lle'	x		x
Haubenberger et al. ^[55]	2011	Digital	Spiral		x	
Bajaj et al. ^[69]	2012	Paper & Pen	Sentence (paper pen)			x
Geny et al. ^[60]	2012	Digital	writing, triangle, '8'		x	
Louis et al. ^[56]	2012	Digital	Spiral		x	
Wagle Shukla et al. ^[82]	2012	Paper & Pen	writing 'p' and 'd' (paper pen)			x
Ma et al. ^[81]	2013	Digital	chinese character			x
Rosenblum et al. ^[35]	2013	Digital	Name and adress	x		x
Louis et al. ^[57]	2014	Digital	Spiral		x	
Michalec et al. ^[58]	2014	Digital	Spiral		x	

**This table is partially based on the literature review of Letanneux et al.^[29]*

1.7. Main findings previous literature

Based on the most important findings of previous studies described above, we conclude that the use of graphical tasks employing a digital tablet seems a suitable method especially to assess bradykinesia and micrographia. When using this method to assess these two important symptoms, 3-dimensional aspects of tremor could also be assessed simultaneously if movement sensors are placed inside the pen which is used to perform the graphical tasks. With regard to graphical tasks, the spiral drawing task seems the most useful to assess tremor. To assess bradykinesia, tracing and copying figures of a predefined size might be most appropriate, because smaller drawing and writing (micrographia) could compensate for the slowness of movement during free drawing and writing tasks. Both duration and velocity are important measures to assess bradykinesia. Micrographia can best be assessed by stroke width and height of the letters 'l' and/or 'e' during sentence writing or during the writing of repeated patterns of these letters. Micrographia is an important symptom in PD patients, however it is not a cardinal symptom. Hence, micrographia should be assessed in combination with other important, cardinal, motor symptoms, such as bradykinesia and tremor.

1.8. Outline of this thesis

In this thesis we study whether a set of graphical tasks can be used for quantitative assessment of motor symptoms of PD, especially to aid in diagnosing and monitoring PD. The main literature findings, as described in the previous section (section 1.3.4), were used to design the standardized tasks and clinical validation studies described in this thesis. Through these activities, we supported the development of the DiPAR handwriting recording system in our studies in the European project 'DiPAR'. Chapter 2 provides an overview of the DiPAR project.

The DiPAR system consists of a sensor-pen (the DiPAR-pen), a digital tablet and an operator computer. The DiPAR-pen was used to perform the standardized graphical tasks, such as handwriting, drawing, and other upper limb tasks, suitable to assess bradykinesia and micrographia. Motion sensors inside the pen allowed 3-dimensional assessment of tremor as well. To improve on previous studies we assessed bradykinesia, tremor and micrographia simultaneously. In four experimental studies we investigated whether our set of standardized graphical tasks, performed with the DiPAR-pen, could be used to

aid in diagnosing and monitoring PD. Several important validation steps in diagnostic research, as described previously (section 1.3), were executed and their results described in the chapters of this thesis. The outline of the chapters in this thesis is as follows:

Chapter 2 – The DiPAR project

This chapter provides an overview of the European research project 'DiPAR' (European 7th Framework programme, Grant agreement 262291). The experimental studies described in this thesis were performed as part of this research project. The full title of the DiPAR project is 'Diagnosing Parkinson's disease by neuromuscular function evaluation'.

Chapter 3 – Standardized handwriting to assess bradykinesia, micrographia and tremor in Parkinson's disease

In this chapter, we investigated whether performance on a set of standardized handwriting and drawing tasks (graphical tasks) differed between PD patients (n=10) and gender and age-matched healthy control (HC) participants (n=10), which is the first important step in diagnostic research^[16]. In this study we calculated measures to assess two cardinal motor symptoms of PD, bradykinesia and tremor, and another common symptom in PD patients, micrographia.

Chapter 4 – Reproducibility of standardized fine motor control tasks and age effects in healthy adults

A second important step in diagnostic research is to assess the reproducibility of test results^[17]. This chapter describes the results of a reproducibility study. We studied the test-retest reliability of our set of graphical tasks in healthy adults of different ages (20–75 years, n=36). Participants performed the tasks twice at the same time and day, with one week in between.

Chapter 5 – Tremor presence and movement time measures help in distinguishing between Essential tremor and Parkinson's disease

Quantitative assessment of motor symptoms of PD could be of additional value in the differentiation between PD and other movement disorders. Therefore, we investigated in this chapter whether our set of graphical tasks can be used to discriminate between PD (n=12), essential tremor (ET, n=13), enhanced physiological tremor (EPT, n=10), functional tremor (FT, n=8), and healthy controls (HC, n=23). Similar to Chapters 3 and 4, we used measures to assess bradykinesia, tremor and micrographia to investigate differences between groups.

Chapter 6 – Graphical tasks to measure upper limb function in patients with Parkinson’s disease: Validity and response to dopaminergic medication

In this chapter we validated our set of graphical tasks, by comparing the test results of PD patients (n=14) to their performance on a reference measure. The Purdue pegboard test was chosen as reference, because it is an already validated test to assess upper limb function. To investigate whether our set of graphical tasks could be used to monitor treatment effects, we studied the changes in performance after medication intake in PD patients. Measures to assess bradykinesia, tremor and micrographia were used again to examine performance and changes in performance in PD patients.

Chapter 7 – Discussion and future directions

In this chapter the advantages and disadvantages of our approach and the results of the experimental clinical studies are discussed in a broader perspective. Recommendations for future research are given to improve the use of graphical tasks for clinical application.

1.9. References

- [1] Massano, J. & Bhatia, K. P. Clinical approach to Parkinson’s disease: features, diagnosis, and principles of management. *Cold Spring Harb. Perspect. Med.* **2**, a008870 (2012).
- [2] Jankovic, J. Parkinson’s disease: clinical features and diagnosis. *J. Neurol. Neurosurg. Psychiatry* **79**, 368–376 (2008).
- [3] Von Campenhausen, S., Bornschein, B., Wick, R., Bötzel, K., Sampaio, C., *et al.* Prevalence and incidence of Parkinson’s disease in Europe. *Eur. Neuropsychopharmacol.* **15**, 473–490 (2005).
- [4] Hughes, A. J., Daniel, S. E., Kilford, L. & Lees, A. J. Accuracy of clinical diagnosis of idiopathic Parkinson’s disease: a clinico-pathological study of 100 cases. *J. Neurol. Neurosurg. Psychiatry* **55**, 181–184 (1992).
- [5] Hughes, A. J., Daniel, S. E., Ben-Shlomo, Y. & Lees, A. J. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. *Brain* **125**, 861–870 (2002).
- [6] Tolosa, E., Wenning, G. & Poewe, W. The diagnosis of Parkinson’s disease. *Lancet Neurol.* **5**, 75–86 (2006).
- [7] Hughes, A., Daniel, S. & Lees, A. Improved accuracy of clinical diagnosis of Lewy body Parkinson’s disease. *Neurology* **57**, 1497–1499 (2001).
- [8] Grosset, D. G. & Schapira, A. H. Timing the initiation of treatment in Parkinson’s disease. *J. Neurol. Neurosurg. Psychiatry* **79**, 615 (2008).
- [9] Goetz, C. G. & Stebbins, G. T. Assuring interrater reliability for the UPDRS motor section: Utility of the UPDRS teaching tape. *Mov. Disord.* **19**, 1453–1456 (2004).

- [10] Goetz, C. G., Poewe, W., Rascol, O. & Christina, S. State of the Art Review The Unified Parkinson's Disease Rating Scale (UPDRS): Status and Recommendations. *Mov. Disord.* **18**, 738–750 (2003).
- [11] Goetz, C. G., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., *et al.* Movement disorder society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): Process, format, and clinimetric testing plan. *Mov. Disord.* **22**, 41–47 (2007).
- [12] Ebersbach, G., Baas, H., Csoti, I., Müngersdorf, M. & Deuschl, G. Scales in Parkinson's disease. *J. Neurol.* **253**, 32–35 (2006).
- [13] Richards, M., Marder, K., Cote, L. & Mayeux, R. Interrater reliability of the Unified Parkinson's Disease Rating Scale motor examination. *Mov. Disord.* **9**, 89–91 (1994).
- [14] Post, B., Merkus, M. P., de Bie, R. M. a, de Haan, R. J. & Speelman, J. D. Unified Parkinson's Disease Rating Scale motor examination: Are ratings of nurses, residents in neurology, and movement disorders specialists interchangeable? *Mov. Disord.* **20**, 1577–1584 (2005).
- [15] Kostek, B., Kaszuba, K., Zwan, P., Robowski, P. & Slawek, J. Automatic assessment of the motor state of the Parkinson's disease patient--a case study. *Diagn. Pathol.* **7**, 18 (2012).
- [16] Sackett, D. . & Haynes, R. . Evidence base of clinical diagnosis - The architecture of diagnostic research. *Br. Med. J.* **322**, 1115–1117 (2001).
- [17] Van den Bruel, A., Cleemput, I., Aertgeerts, B., Ramaekers, D. & Buntinx, F. The evaluation of diagnostic tests: evidence on technical and diagnostic accuracy, impact on patient outcome and cost-effectiveness is needed. *J. Clin. Epidemiol.* **60**, 1116–1122 (2007).
- [18] Dickson, J. M. & Grünewald, R. a. Somatic symptom progression in idiopathic Parkinson's disease. *Park. Relat. Disord.* **10**, 487–492 (2004).
- [19] Schelosky, L. & Poewe, W. Topographical onset and progression of motor symptoms in idiopathic parkinson's disease. *Mov. Disord.* **5**, 13 (1990).
- [20] Lacy, S. E., Lones, M. A & Smith, S. L. Characterisation of Movement Disorder in Parkinson's Disease using Evolutionary Algorithms Categories and Subject Descriptors. *Proceedings of the Genetic and Evolutionary Computation Conference* 1479–1485 (2013).
- [21] Espay, A. J., Beaton, D. E., Morgante, F., Gunraj, C. a., Lang, A. E., *et al.* Impairments of speed and amplitude of movement in Parkinson's disease: A pilot study. *Mov. Disord.* **24**, 1001–1008 (2009).
- [22] Heldman, D. a., Giuffrida, J. P., Chen, R., Payne, M., Mazzella, F., *et al.* The modified bradykinesia rating scale for Parkinson's disease: Reliability and comparison with kinematic measures. *Mov. Disord.* **26**, 1859–1863 (2011).
- [23] Heldman, D. A., Espay, A. J., LeWitt, P. A. & Giuffrida, J. P. Clinician versus machine: Reliability and responsiveness of motor endpoints in Parkinson's disease. *Park. Relat. Disord.* **20**, 590–595 (2014).

- [24] Kim, J.-W., Lee, J.-H., Kwon, Y., Kim, C.-S., Eom, G.-M., *et al.* Quantification of bradykinesia during clinical finger taps using a gyrosensor in patients with Parkinson's disease. *Med. Biol. Eng. Comput.* **49**, 365–71 (2011).
- [25] Ling, H., Massey, L. A., Lees, A. J., Brown, P. & Day, B. L. Hypokinesia without decrement distinguishes progressive supranuclear palsy from Parkinson's disease. *Brain* **135**, 1141–1153 (2012).
- [26] Shima, K., Tsuji, T., Kan, E., Kandori, A., Yokoe, M., *et al.* Measurement and evaluation of finger tapping movements using magnetic sensors. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* **2008**, 5628–31 (2008).
- [27] Koop, M. M., Shivitz, N. & Brontë-Stewart, H. Quantitative measures of fine motor, limb, and postural bradykinesia in very early stage, untreated Parkinson's disease. *Mov. Disord.* **23**, 1262–8 (2008).
- [28] Salarian, A., Russmann, H., Wider, C., Burkhard, P. R., Vingerhoets, F. J. G., *et al.* Quantification of tremor and bradykinesia in Parkinson's disease using a novel ambulatory monitoring system. *IEEE Trans. Biomed. Eng.* **54**, 313–322 (2007).
- [29] Letanneux, A., Danna, J., Velay, J.-L., Viallet, F. & Pinto, S. From micrographia to Parkinson's disease dysgraphia. *Mov. Disord.* **29**, 1467–1475 (2014).
- [30] Van Gemmert, a W., Teulings, H. L., Contreras-Vidal, J. L. & Stelmach, G. E. Parkinson's disease and the control of size and speed in handwriting. *Neuropsychologia* **37**, 685–694 (1999).
- [31] Tucha, O., Mecklinger, L., Thome, J., Reiter, A., Alders, G. L., *et al.* Kinematic analysis of dopaminergic effects on skilled handwriting movements in Parkinson's disease. *J. Neural Transm.* **113**, 609–623 (2006).
- [32] Poluha, P. C., Teulings, H. L. & Brookshire, R. H. Handwriting and speech changes across the levodopa cycle in Parkinson's disease. *Acta Psychol.* **100**, 71–84 (1998).
- [33] Lange, K. W., Mecklinger, L., Walitza, S., Becker, G., Gerlach, M., *et al.* Brain dopamine and kinematics of graphomotor functions. *Hum. Mov. Sci.* **25**, 492–509 (2006).
- [34] Bidet-Ildei, C., Pollak, P., Kandel, S., Fraix, V. & Orliaguet, J. P. Handwriting in patients with Parkinson disease: Effect of l-dopa and stimulation of the subthalamic nucleus on motor anticipation. *Hum. Mov. Sci.* **30**, 783–791 (2011).
- [35] Rosenblum, S., Samuel, M., Zlotnik, S., Erikh, I. & Schlesinger, I. Handwriting as an objective tool for Parkinson's disease diagnosis. *J. Neurol.* **260**, 2357–2361 (2013).
- [36] Eichhorn, T. E. & Gasser, T. Computational Analysis of Open Loop Handwriting Movements in Parkinson's Disease : A Rapid Method to Detect Dopamine tic Effects. *Mov. Disord.* **11**, 289–297 (1996).
- [37] Banaszkiwicz, K., Rudzińska, M., Bukowczan, S., Izvorski, A. & Szczudlik, A. Spiral drawing time as a measure of bradykinesia. *Neurol. Neurochir. Pol.* **43**, 16–21 (2009).
- [38] Broderick, M. P., Van Gemmert, A. W. A., Shill, H. a & Stelmach, G. E. Hypometria and bradykinesia during drawing movements in individuals with Parkinson's disease. *Exp. Brain Res.* **197**, 223–33 (2009).

- [39] Helmich, R. C., Hallett, M., Deuschl, G., Toni, I. & Bloem, B. R. Cerebral causes and consequences of parkinsonian resting tremor: A tale of two circuits? *Brain* **135**, 3206–3226 (2012).
- [40] Thenganatt, M. A. & Jankovic, J. Parkinson disease subtypes. *JAMA Neurol.* **71**, 499–504 (2014).
- [41] Deuschl, G., Bain, P. & Brin, M. Consensus Statement of the Movement Disorder Society on Tremor. *Mov. Disord.* **13**, 2–23 (2008).
- [42] Bötzel, K., Tronnier, V. & Gasser, T. The differential diagnosis and treatment of tremor. *Dtsch. Arztebl. Int.* **111**, 225–36 (2014).
- [43] Farkas, Z., Csillik, A., Szirmai, I. & Kamondi, A. Asymmetry of tremor intensity and frequency in Parkinson's disease and essential tremor. *Park. Relat. Disord.* **12**, 49–55 (2006).
- [44] Papapetropoulos, S., Katzen, H. L., Scanlon, B. K., Guevara, A., Singer, C., *et al.* Objective quantification of neuromotor symptoms in Parkinson's disease: implementation of a portable, computerized measurement tool. *Parkinsons. Dis.* **2010**, Article ID 760196 (2010).
- [45] Muthuraman, M., Hossen, A., Heute, U., Deuschl, G. & Raethjen, J. A new diagnostic test to distinguish tremulous Parkinson's disease from advanced essential tremor. *Mov. Disord.* **26**, 1548–52 (2011).
- [46] Wile, D. J., Ranawaya, R. & Kiss, Z. H. T. Smart watch accelerometry for analysis and diagnosis of tremor. *J. Neurosci. Methods* **230**, 1–4 (2014).
- [47] Bhidayasiri, R., Petchrutchatachart, S., Pongthornseri, R., Anan, C., Dummin, S., *et al.* Low-Cost, 3-dimension, office-based inertial sensors for automated tremor assessment: Technical development and experimental verification. *J. Parkinsons. Dis.* **4**, 273–282 (2014).
- [48] Elble, R. J., Brilliant, M., Leffler, K. & Higgins, C. Quantification of essential tremor in writing and drawing. *Mov. Disord.* **11**, 70–78 (1996).
- [49] Pullman, S. L. Spiral analysis: a new technique for measuring tremor with a digitizing tablet. *Mov. Disord.* **13 Suppl 3**, 85–89 (1998).
- [50] Ondo, W. G., Wang, A., Thomas, M. & Vuong, K. D. Evaluating factors that can influence spirography ratings in patients with essential tremor. *Park. Relat. Disord.* **11**, 45–48 (2005).
- [51] Miralles, F., Tarongí, S. & Espino, a. Quantification of the drawing of an Archimedes spiral through the analysis of its digitized picture. *J. Neurosci. Methods* **152**, 18–31 (2006).
- [52] Ulmanová, O., Homann, C. N., Ulman, R., Jech, R., Čapek, V., *et al.* Tremor magnitude: A single index to assess writing and drawing in essential tremor. *Park. Relat. Disord.* **13**, 250–253 (2007).
- [53] Saunders-Pullman, R., Derby, C., Stanley, K., Floyd, A., Bressman, S., *et al.* Validity of spiral analysis in early Parkinson's disease. *Mov. Disord.* **23**, 531–537 (2008).
- [54] Kraus, P. H. & Hoffmann, A. Spiralometry: computerized assessment of tremor amplitude on the basis of spiral drawing. *Mov. Disord.* **25**, 2164–70 (2010).

- [55] Haubenberger, D., Kalowitz, D., Nahab, F. B., Toro, C., Ippolito, D., *et al.* Validation of digital spiral analysis as outcome parameter for clinical trials in essential tremor. *Mov. Disord.* **26**, 2073–80 (2011).
- [56] Louis, E. D., Zhao, Q., Meng, H. & Ding, D. Screening for action tremor in epidemiological field surveys: assessing the reliability of a semi-quantitative, visual, template-based scale for rating hand-drawn spirals. *Tremor Other Hyperkinet. Mov. (N. Y.)* **2**, 1–6 (2012).
- [57] Louis, E. D., Michalec, M. & Gillman, A. Shaky drawing: what is the rate of decline during prospective follow-up of essential tremor? *BMJ Open* **4**, e004626 (2014).
- [58] Michalec, M., Hernandez, N., Clark, L. N. & Louis, E. D. The spiral axis as a clinical tool to distinguish essential tremor from dystonia cases. *Park. Relat. Disord.* **20**, 541–544 (2014).
- [59] Accardo, A., Chiap, A., Marino, S., Lanzafame, P. & Bramanti, P. Kinematic analysis of tremor - biomed 2010. *Biomed. Sci. Instrum.* **46**, 347–361 (2010).
- [60] Geny, C., Coste, C. A., Gabelle, A., Fattal, C., Poignet, P., *et al.* Contribution of different drawing tasks in the assessment of ET. *Eur. J. Neurol.* **19**, P2653 458–807 (2012).
- [61] Blank, R., Miller, V. & Voû, H. Von. Human motor development and hand laterality: a kinematic analysis of drawing movements. *Neurosci. Lett.* **295**, 89–92 (2000).
- [62] Zietsma, R. C. Designing a comprehensive system for analysis of handwriting biomechanics in relation to neuromotor control of handwriting (PhD thesis). (University of Strathclyde, Glasgow, 2010). at <<http://www.strath.ac.uk/library/>>
- [63] McLennan, J. E., Nakano, K., Tyler, H. R. & Schwab, R. S. Micrographia in Parkinson's Disease. *J. Neurol. Sci.* **15**, 141–152 (1972).
- [64] Kim, E. J., Lee, B. H., Park, K. C., Lee, W. Y. & Na, D. L. Micrographia on free writing versus copying tasks in idiopathic Parkinson's disease. *Park. Relat. Disord.* **11**, 57–63 (2005).
- [65] Ponsen, M. M., Daffertshofer, A., Wolters, E. C., Beek, P. J. & Berendse, H. W. Impairment of complex upper limb motor function in de novo Parkinson's disease. *Parkinsonism Relat. Disord.* **14**, 199–204 (2008).
- [66] Wagle Shukla, A., Ounpraseuth, S., Okun, M. S., Gray, V., Schwankhaus, J., *et al.* Micrographia and related deficits in Parkinson's disease: a cross-sectional study. *BMJ Open* **2**, e000628 (2012).
- [67] Contreras-Vidal, J. L., Teulings, H. L. & Stelmach, G. E. Micrographia in Parkinson's disease. *Neuroreport* **6**, 2089–2092 (1995).
- [68] Ondo, W. G. & Satija, P. Withdrawal of visual feedback improves micrographia in Parkinson's disease. *Mov. Disord.* **22**, 2130–2131 (2007).
- [69] Bajaj, N. P. S., Wang, L., Gontu, V., Grosset, D. G. & Bain, P. G. Accuracy of subjective and objective handwriting assessment for differentiating Parkinson's disease from tremulous subjects without evidence of dopaminergic deficits (SWEDDs): an FP-CIT-validated study. *J. Neurol.* **259**, 2335–2340 (2012).

- [70] Oliveira, R. M., Gurd, J. M., Nixon, P., Marshall, J. C. & Passingham, R. E. Micrographia in Parkinson's disease: the effect of providing external cues. *J. Neurol. Neurosurg. Psychiatry* **63**, 429–433 (1997).
- [71] Teulings, H. L., Contreras-Vidal, J. L., Stelmach, G. E. & Adler, C. H. Parkinsonism reduces coordination of fingers, wrist, and arm in fine motor control. *Exp. Neurol.* **146**, 159–170 (1997).
- [72] Van Gemmert, A. W., Teulings, H. L. & Stelmach, G. E. Parkinsonian patients reduce their stroke size with increased processing demands. *Brain Cogn.* **47**, 504–512 (2001).
- [73] Contreras-Vidal, J. L., Teulings, H. L., Stelmach, G. E. & Adler, C. H. Adaptation to changes in vertical display gain during handwriting in Parkinson's disease patients, elderly and young controls. *Park. Relat. Disord.* **9**, 77–84 (2002).
- [74] Teulings, H. L., Contreras-Vidal, J. L., Stelmach, G. E. & Adler, C. H. Adaptation of handwriting size under distorted visual feedback in patients with Parkinson's disease and elderly and young controls. *J. Neurol. Neurosurg. Psychiatry* **72**, 315–324 (2002).
- [75] Van Gemmert, A. W. A., Adler, C. H. & Stelmach, G. E. Parkinson's disease patients undershoot target size in handwriting and similar tasks. *J. Neurol. Neurosurg. Psychiatry* **74**, 1502–1508 (2003).
- [76] Teulings, H. L. & Stelmach, G. E. Control of stroke size, peak acceleration, and stroke duration in Parkinsonian handwriting. *Hum. Mov. Sci.* **10**, 315–334 (1991).
- [77] Contreras-Vidal, J. L., Poluha, P., Teulings, H. L. & Stelmach, G. E. Neural dynamics of short and medium-term motor control effects of levodopa therapy in Parkinson's disease. *Artif. Intell. Med.* **13**, 57–79 (1998).
- [78] Van Gemmert, A. W., Teulings, H. L. & Stelmach, G. E. The influence of mental and motor load on handwriting movements in parkinsonian patients. *Acta Psychol.* **100**, 161–175 (1998).
- [79] Siebner, H. R., Ceballos-baumann, A., Standhardt, H., Auer, C., Conrad, B., *et al.* Changes in Handwriting Resulting From Bilateral High-Frequency Stimulation of the Subthalamic Nucleus in Parkinson's Disease. *Mov. Disord.* **14**, 964–971 (1999).
- [80] Caligiuri, M. P., Teulings, H. L., Filoteo, J. V., Song, D. & Lohr, J. B. Quantitative measurement of handwriting in the assessment of drug-induced parkinsonism. *Hum. Mov. Sci.* **25**, 510–522 (2006).
- [81] Ma, H. I., Hwang, W. J., Chang, S. H. & Wang, T. Y. Progressive micrographia shown in horizontal, but not vertical, writing in Parkinson's disease. *Behav. Neurol.* **27**, 169–174 (2013).
- [82] Wagle Shukla, A., Ounpraseuth, S., Okun, M. S., Gray, V., Schwankhaus, J., *et al.* Micrographia and related deficits in Parkinson's disease: a cross-sectional study. *BMJ Open* **2**, 1–7 (2012).

