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

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# CHAPTER 6

## GRAPHICAL TASKS TO MEASURE UPPER LIMB FUNCTION IN PATIENTS WITH PARKINSON'S DISEASE: VALIDITY AND RESPONSE TO DOPAMINERGIC MEDICATION

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## 6.1. Abstract

The most widely used method to assess motor functioning in Parkinson's disease (PD) patients is the Unified Parkinson's Disease Rating Scale-III (UPDRS-III). The UPDRS-III has limited ability to detect subtle changes in motor symptoms. Alternatively, graphical tasks can be used to provide objective measures of upper limb motor dysfunction. The present study investigated the validity of such graphical tasks to assess upper limb function in PD patients and their ability to detect subtle changes in performance. Fourteen PD patients performed graphical tasks before and after taking dopaminergic medication. Graphical tasks included figure tracing, writing and a modified Fitts' task. The Purdue pegboard test was performed to validate these graphical tasks. Movement time (MT), writing size and the presence of tremor were assessed. MT on the graphical tasks correlated significantly with performance on the Purdue pegboard test (Spearman's  $\rho > 0.65$ ;  $p < 0.05$ ). MT decreased significantly after the intake of dopaminergic medication. Tremor power decreased after taking dopaminergic medication in most PD patients who suffered from tremor. Writing size did not correlate with performance on the Purdue pegboard test, nor did it change after taking medication. Our set of graphical tasks is valid to assess upper limb function in PD patients. MT proved to be the most useful measure for this purpose. The response on dopaminergic medication was optimally reflected by an improved MT on the graphical tasks in combination with a decreased tremor power, whereas writing size did not respond to dopaminergic treatment.

## 6.2. Introduction

Correct diagnosis of Parkinson's disease (PD), a neurodegenerative movement disorder, is essential for optimal treatment and prognosis. Diagnosis is based upon the cardinal motor symptoms of PD: bradykinesia (slow movement), rigidity (muscle stiffness), resting tremor (trembling of a body part in rest) and postural and gait impairment<sup>[1]</sup>. The motor part (part III) of the most recent revision of the Unified Parkinson's Disease Rating Scale by the Movement Disorder Society (MDS-UPDRS-III) is the most widely used scale in clinical practice to assess parkinsonian symptoms<sup>[1,2]</sup>. However, the MDS-UPDRS-III has several limitations. Firstly, the MDS-UPDRS-III needs to be evaluated by a trained assessor, which makes it less suitable for home-based monitoring. Secondly, the inter-rater reliability is high for movement disorders specialists, but unfortunately not all patients have access to specialized movement disorder centres, which negatively influences the accuracy and reliability of the MDS-UPDRS-III. Thirdly, the MDS-UPDRS-III has limited ability to detect subtle changes in motor function, which are common in early PD. Therefore, an objective, sensitive, reliable and accurate assessment system could potentially overcome these limitations of the existing MDS-UPDRS-III scale.

Objective motor assessment systems have been developed previously, such as Kinesia (Great Lakes NeuroTechnologies, USA)<sup>[3,4]</sup> and Parkinson's KinetiGraph (PKG, Global Kinetics Corporation, Australia). These systems involve movement sensors that need to be worn on the index finger (Kinesia) or wrist (PKG) and are used to assess and monitor movement of the upper limb. Another tool which might be useful for monitoring employs a digital tablet and pen and can be used to perform and record graphical tasks, i.e. handwriting and drawing<sup>[5]</sup>. Similar to the Kinesia and PKG systems, the pen and tablet tool is non-invasive, portable, and can be used easily at home without an examiner. An advantage of Kinesia and a digital tablet compared to PKG is that specific short-term tasks can be performed several times a day and that patients don't have to wear a sensor for multiple days. An advantage of a digital tablet when compared to Kinesia is that a clinician can obtain feedback on how tasks were performed, because pen-tip movements are recorded. On the contrary, if a patient performs a task while wearing the Kinesia-sensor, like holding the arms in a specific posture, there is no way to verify whether the task was performed correctly.

Graphical tasks employing a digital tablet provide objective measures of important motor symptoms of PD and were used previously to show differences between PD patients and healthy control (HC) participants<sup>[6-10]</sup>. Medication

effects have also been investigated in PD patients using such a set-up<sup>[11-15]</sup>. In general, these studies investigated one graphical task. However, to assess and monitor PD, it is important to measure several aspects of motor behaviour, because PD patients do not always suffer from the same combination of symptoms, and treatment could have variable effects on different aspects of motor functioning of PD patients. Therefore, the assessment battery of the current study consists of several graphical tasks, providing useful measures for bradykinesia, tremor and micrographia<sup>[6]</sup>. A newly developed system consisting of a pen and tablet and custom software, based on a concept by Manus Neurodynamica Ltd, was used. The advantage of this system is that it includes an integrated comprehensive sensor and data acquisition system for highly accurate recordings and analysis. The aim of the current study was to investigate the validity of these graphical tasks to assess upper limb function in PD patients. Validity of comparable methods in the literature is mostly determined by their correlation with the total UPDRS-III<sup>[11,16-19]</sup>. However, our graphical tasks only involve movements of the upper limb, and since the MDS-UPDRS-III score involves more than just upper limb functioning, it is less suitable for validation. Therefore, a validated test for upper limb functioning<sup>[17,20,21]</sup>, the Purdue pegboard test (PPT), was used as reference, in addition to MDS-UPDRS-III scores, involving hand items only.

Graphical tasks in this study include simple tracing and writing tasks and a modified Fitts' task, which are easy to perform and cover a large range of upper limb functions. A resting task was included to measure resting tremor, because PD tremor is typically a resting tremor<sup>[22]</sup>. Furthermore the modified Fitts' task was used to assess the speed-accuracy trade off, which may be impaired in PD patients<sup>[23]</sup>. This exploratory study investigated which of the tasks could be used most optimally to assess upper limb motor functioning and to detect changes in motor performance after use of dopaminergic medication in PD patients.

## **6.3. Methods**

### *6.3.1. Participants*

Fourteen PD patients performed the tasks with their right hand. PD patients were diagnosed by a movement disorders specialist (according to the UK Parkinson's Disease Society Brain Bank criteria<sup>[24]</sup>) and were treated at the movement disorders clinic of the University Medical Center Groningen (UMCG). Since the patients had to be able to hold a pen for at least 30 minutes and perform

tracing and writing tasks, PD patients in relatively early stages of the disease (Hoehn and Yahr stages 1–2<sup>[25]</sup>) were selected. Table 6.1 provides a summary of the PD patient characteristics. Patients agreed with overnight withdrawal of their usual dose of dopaminergic medication. Exclusion criteria were a neurological or motor disorder other than PD and a low score (<26) on the Mini Mental State Examination (MMSE) to ensure understanding of task instructions. All patients signed informed consent and the protocol was approved by the Medical Ethical Committee of the UMCG.

### 6.3.2. *Experimental design*

Patients were seated in front of a table in a comfortable position to write. A tablet computer (ASUS Eee Slate EP121) and a newly developed digital pen with custom software were used. Position of the pen-tip on the tablet and gyroscope signals in three directions (pitch, yaw and roll) was recorded. All recordings had a sampling frequency of 200 Hz. The pen had a wireless connection to the tablet. Patients performed seven tasks (see below). The examiner was seated behind an operator computer to start and stop recordings and determined whether patients executed the tasks correctly. If a task was executed incorrectly, the recording was stopped and restarted after re-instruction. The OFF measurement was performed in the morning, after overnight withdrawal of medication. Thereafter, patients took their medication and had a one-hour break, to allow for an optimal medication effect. After one hour the ON measurement was performed. The hand items of the MDS-UPDRS-III were assessed and videotaped and scored by a clinician from the UMCG (RWKB), who was blinded to the medication status of the patients.

Table 6.1. Summary of PD patient characteristics

ID	Gender	Age	MMSE	Diagnosis	Years since diagnosis	H&Y	MDS-UPDRS-III				Purdue pegboard	
							Bradykinesia subscore		Tremor subscore		Right hand	
							OFF	ON	OFF	ON	OFF	ON
PD001	M	73	26	PD	3	2	1 <sup>a</sup>	0 <sup>b</sup>	0 <sup>c</sup>	0 <sup>c</sup>	9	9
PD002	M	78	29	PD	4	1	0 <sup>a</sup>	0	0 <sup>c</sup>	0	11	11
PD003	M	60	28	PD	2	2	6	0	0 <sup>c</sup>	0	7	8
PD004	M	81	29	PD	0	2	0	1	0	0	8	8
PD005	F	70	29	PD	3	2	1	0	0 <sup>d</sup>	0	12	13
PD006	M	69	28	PD	10	2	1	1	0	0	8	4
PD007	F	76	30	PD	1	2	0	0	0	0	8	9
PD008	F	68	26	PD	1	2	3	**	0	**	7	7
PD009	M	69	30	PD	10	2	2	0	0	0	7	8
PD010	M	67	29	PD	6	1	0	0	0	0	11	11
PD011	F	50	28	PD	8	2	0	0	2	0	12	13
PD012	M	66	30	tdPD	5	2	0	1	0	0 <sup>d</sup>	7	11
PD013	M	73	27	tdPD	7	2	0	2	3	3	8	7
PD014	M	61	26	tdPD	5	2	2	3	0	0	10	11

MMSE = Mini Mental State Examination; PD = Parkinson's disease; tdPD = Tremor dominant Parkinson's Disease; H&Y = Hoehn and Yahr score; OFF = off medication, after overnight withdrawal of anti-parkinsonian medication; ON = on medication, 1 hour after taking medication; Med = Medication; MDS-UPDRS-III = the motor part (part III) of the Movement Disorder Society revision of the Unified Parkinson's Disease Rating Scale; Bradykinesia subscore = sum of right hand items on 'finger tapping', 'hand movements', and 'pronation-supination movement of the hand'; Tremor subscore = sum of right hand tremor-items. a) For these patients the 'Hand movements' score of the right hand was missing. b) For this patients the 'Finger tapping' score of the right hand was missing. c) For these patients the 'Kinetic tremor' scores for the right hand were missing d. For these patients the 'Postural tremor' score of the right hand was missing. \*\*For this patient too many items were missing.

### 6.3.3. Tasks

Patients were instructed to start each task after a signal of the examiner. Firstly, a recording at rest (30 seconds) was performed. Patients were seated with the right elbow resting on the table, the hand resting on the tablet and the pen-tip touching a target (filled circle, 0.7 cm in diameter) in the center of the tablet. Next, the patients subsequently traced circle, spiral and zigzag figures which were displayed on the tablet (see Figure 6.1). The circle and spiral were traced ten times in a clockwise direction, starting from the 12 o'clock position (circle) or from inside to outside (spiral). The zigzag was traced five times, from left to right and back.

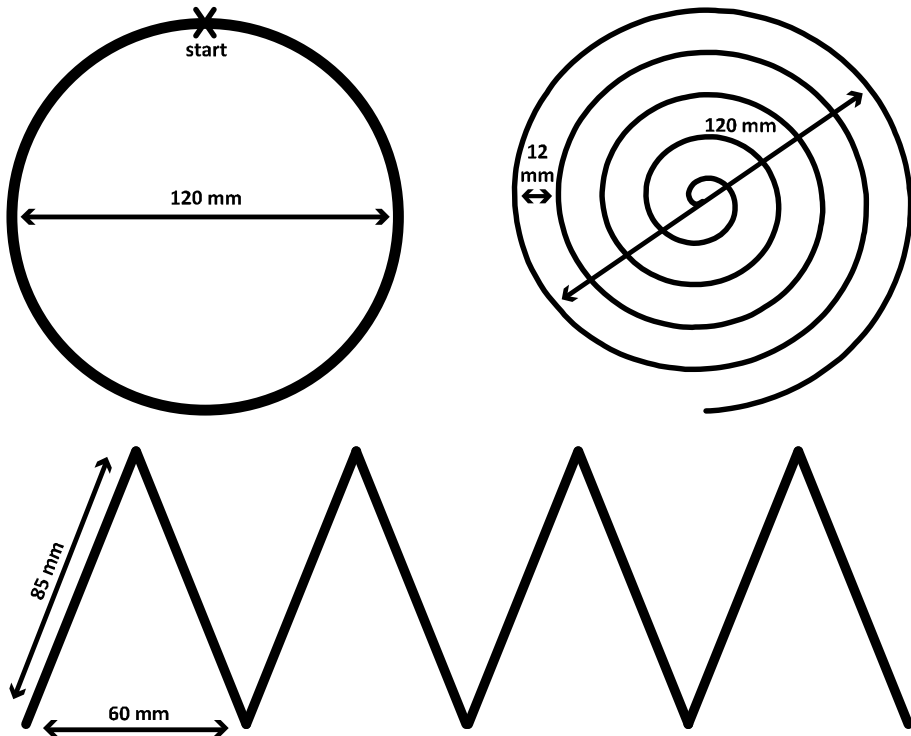


Figure 6.1. Templates and their dimensions for the tracing tasks: a circle, spiral and zigzag figure.

The next task consisted of writing 'elelelel' five times with each phrase starting at the left side of the tablet with visual feedback on the screen. An example was provided on paper on the table above the tablet. Thereafter, a modified Fitts' task was performed, which was similar to Fitts' original task<sup>[26]</sup> but adapted to the



dimensions of our system. Patients touched two targets (filled circles, placed on an imaginary horizontal line in the middle of the tablet) alternately with the pen-tip as fast and as accurately as possible (20 seconds). The distance between the targets was 7 cm for subtasks 1 to 4 and 20 cm for subtasks 5 to 8, while the diameter of the targets increased (0.7, 1.3, 1.9, 2.5 cm). Finally, the PPT was performed, which employed a board with a vertically oriented row with 25 holes and metal pins located in a reservoir at the top. We limited the PPT to the right hand task, similar to the other graphical tasks. Patients were instructed to place as many pins as possible in the holes within 30 seconds. Participants were allowed to practice before the test<sup>[27]</sup>.

#### 6.3.4. Data analysis

Graphical tasks were analysed using Matlab (R2014A). Mean movement time (MT) per trial was calculated for the tracing tasks (CircleMT; SpiralMT and ZigzagMT), using the x and y coordinates of the pen-tip.

##### 'elelele' writing task

The pen-tip position data (x and y coordinates) were preprocessed. First, the data were split into separate segments, where each segment represented one line of text. This was done using an 'in range' signal, which indicates whether or not the pen is in detection range of the tablet employing that, after writing one line of text, the patient lifts the pen so that it is outside the detection range of the tablet. Subsequently, the segments corresponding to an 'e' or an 'l' were identified. The shapes in each line were recognized by using a state machine that employs the direction of change of the pen-tip position as input (similar to the method used in<sup>[6]</sup>, see Appendix 2). For each detected letter 'e' and 'l', movement time (MT) was calculated by counting the samples and dividing it by 200 (since the sample frequency was 200 Hz). MT was averaged over all detected 'e's' and 'l's', resulting in the features E\_MT and L\_MT. The mean width and height of the letters was also calculated, using the x and y coordinates of the pen-tip (E\_Width; E\_Height; L\_Width; L\_Height).

##### Modified Fitts task analysis

The modified Fitts' task was analysed according to Fitts' law<sup>[26]</sup>. The tradeoff between speed and accuracy was modelled by Fitts<sup>[26]</sup> in the time required for movement (T):

$$T = a + b \left( \log \frac{2A}{D} \right)$$

here,  $A$  is the distance between targets and  $D$  the target diameter. The part  $\log(2A/D)$  is known as the index of difficulty (ID). When multiple IDs are available,  $a$  and  $b$  can be estimated by linear regression. In our modified Fitts' task eight IDs could be determined, since the task consists of eight subtasks, with varying difficulty. For each patient the mean  $T$  for each ID (each subtask) was calculated as the average time needed to move the pen from one target to the other, to allow determination of the relationship between movement time and ID. A linear curve was then fitted to the data points and a least squares calculation was used to determine the goodness of fit (FittsR2). FittsR2 refers to the degree of compliance with Fitts' law and was determined for each patient. The slope of the fitted curve (FittsSlope) describes the extent to which the performance becomes slower with an increase in ID and was calculated for each patient, as well.

### Tremor analysis

For the resting, circle, and spiral tasks the gyroscope signals were analysed to assess tremor. In detail, the procedure to extract tremor features consists of the following steps:

- The gyroscope signals were filtered with a 5 samples long running median filter to remove artefactual peaks.
- To dampen the lowest frequencies (<3 Hz) to remove the frequency components not related to tremor, the gyroscope signals were filtered by removing the output of a second order Savitzky-Golay filter. The frame size of the filter is 0.33 times the sample rate of the signal for the circle and spiral tasks and 0.5 times the sample rate for the rest task. This filtering process increases the signal to noise ratio for the determination of the dominant tremor frequency.
- A principal component analysis was performed on the three filtered gyroscope signals (pitch, yaw and roll) only for the periods in which the patient was performing the task. Then, the first principal component was selected.
- Next, the power spectral density (PSD) of the first principal component was estimated using Welch's method (3 s segments with 2 s overlap, Fourier transform length of 2048 samples) and the band power in a 1 Hz band around each frequency (overlapping bins) was computed.
- The PSD plots were inspected to determine whether PD patients showed tremor during the tasks. This was done by visually checking whether a clear peak between 4 and 9 Hz (typical tremor band<sup>[28]</sup>) was present in the PSD

plot. Only the PD patients who did show a clear peak were selected for further analysis.

- The frequency with the highest band power was selected as the tremor frequency for the PD patients who were selected in the previous step. The relative power (RT) band was calculated by dividing the power in the 1 Hz band around the peak frequency by the total power.

### Statistical analysis

Statistical analyses were conducted using SPSS (IBM SPSS Statistics 22). Normality of measures was assessed by the Shapiro-Wilk test. Validity was estimated by analysing the correlation between performance on the graphical tasks and on the PPT. The PPT yields scores of ordinal level and therefore the correlation between PPTright and the tracing, writing and modified Fitts' task measures was analysed by Spearman's rank correlation. The correlation between performance on the graphical tasks and the MDS-UPDRS-III-bradykinesia subscore was also assessed. A Spearman's rank correlation coefficient between 0.90 and 1.00 was regarded as a very high correlation, between 0.70 and 0.90 as a high correlation, between 0.50 and 0.70 as a moderate correlation, between 0.30 and 0.50 as a low correlation and below 0.30 as a negligible correlation<sup>[29]</sup>. Response to dopaminergic medication was determined by a significant improvement on the movement time, writing size, FittsSlope and FittsR2 and tremor measures after taking dopaminergic medication, by a paired t-test for normally distributed measures or a related-samples Wilcoxon signed rank test, otherwise.

## **6.4. Results**

All PD patients (N=14, mean age 68 years, 10 male; see Table 6.1) completed the tasks OFF and ON medication. Some patients, who had missing data due to a technical problem, were excluded from statistical analysis (see Table 6.2). There was no significant difference between the MDS-UPDRS-III-bradykinesia subscore OFF and ON medication.

### *6.4.1. Validity*

MT on the circle, spiral and zigzag tasks correlated significantly with the PPTright score: CircleMT ( $\rho=-0.69$ ,  $p<0.001$ ), SpiralMT ( $\rho=-0.63$ ,  $p<0.001$ ) and ZigzagMT ( $\rho=-0.66$ ,  $p<0.001$ ). The MT measures of the 'elelelel' writing task showed low correlations with the PPTright score (E\_MT:  $\rho=-0.33$ ,  $p=0.08$  and

L\_MT:  $\rho=-0.37$ ,  $p=0.05$ ). None of the writing size measures correlated with the PPTright score. FittsSlope correlated moderately with the PPTright score ( $\rho=0.64$ ,  $p<0.001$ ) while FittsR2 did not correlate with the PPTright score. Figure 2 shows two examples of the relationship between the PPTright score and graphical task measures. None of the graphical task measures correlated with the MDS-UPDRS-III-bradykinesia subscore.

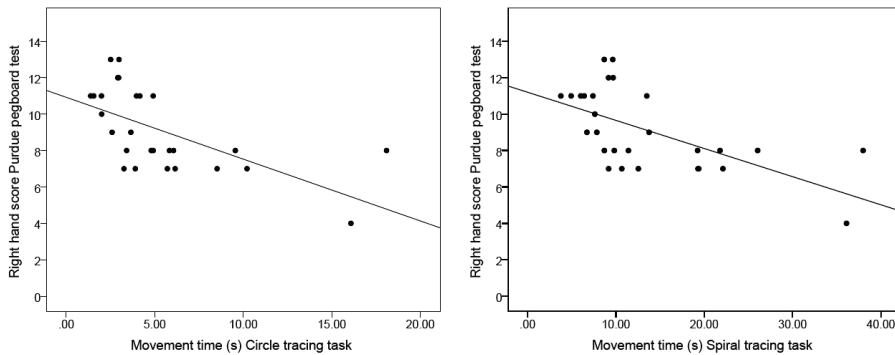


Figure 6.2. Scatterplots and regression lines for the right hand score on the Purdue pegboard test against movement time on the circle tracing task (Upper plot; Spearman’s  $\rho = -0.69$ ) and against movement time on the spiral tracing task (Bottom plot; Spearman’s  $\rho = -0.63$ ).

#### 6.4.2. Response to dopaminergic medication

Table 6.2 provides the test statistics for the response to dopaminergic medication. CircleMT, SpiralMT, E\_MT, L\_MT and FittsSlope were significantly lower at ON medication as compared to OFF medication (related-samples Wilcoxon signed rank test,  $p<0.05$ ). The other measures did not respond to dopaminergic medication.

Table 6.2. Test statistics of the response to dopaminergic medication. Median and interquartile range (iqr) values are provided for both 'on' (ON) and 'off' medication (OFF)

	OFF	ON	Z-value <sup>a</sup>	p-value
CircleMT (s) <sup>b</sup>	4.16 (5.56)	4.12 (3.39)	-2.55	0.01*
SpiralMT (s)	11.42 (10.12)	9.74 (10.93)	-2.61	0.01**
ZZMT (s) <sup>c</sup>	11.92 (3.81)	11.55 (8.04)	-1.18	0.24
E_MT (s)	0.39 (0.12)	0.36 (0.14)	-2.17	0.03*
L_MT (s)	0.52 (0.22)	0.48 (0.13)	-2.67	0.01**
E_width (mm)	9.23 (2.83)	7.79 (4.46)	-0.41	0.68
E_height (mm)	14.87 (7.79)	15.26 (11.06)	-0.22	0.83
L_width (mm)	12.84 (7.58)	12.81 (11.05)	-0.03	0.97
L_height (mm)	39.14 (18.86)	41.20 (26.12)	-0.03	0.97
FittsSlope <sup>d</sup>	0.14 (0.09)	0.12 (0.08)	-2.22	0.03*
FittsR2 <sup>d</sup>	0.89 (0.16)	0.93 (0.08)	-1.87	0.09

MT = Movement Time. a) Results of the related-samples Wilcoxon signed rank test. b) Data of PD007 was missing, due to a technical problem. c) Data of PD002 and PD006 are missing, due to a technical problem. d) Data of PD001, PD002 and PD003 was missing, due to a technical problem. \*statistically significant at  $\alpha = 0.05$ ; \*\*statistically significant at  $\alpha = 0.01$

#### 6.4.3. Tremor assessment

If patients did not suffer from tremor during the graphical tasks, the tremor (peak) frequency could not be determined. Further analysis was therefore only performed on patients exhibiting tremor during at least one of the tasks, indicated by the availability of tremor frequencies. This group was too small to perform statistical analysis, so we investigated each of the patients individually. Table 6.3 shows the results of the tremor analysis. Two patients exhibited tremor during the resting task at OFF medication, six patients during the circle task at OFF medication, and five patients during the spiral task at OFF medication. In general, RP decreased after taking medication and for most of the patients no tremor frequency was seen during the ON medication phase. Patient PD008 showed tremor during the resting task at ON medication, while RP clearly decreased. Tremor frequencies for PD013 during the circle and spiral tasks were available at ON medication, while RP did not clearly decrease. Only PD011 and PD013 had a MDS-UPDRS-III-tremor score higher than 0 (see Table 6.3).

Table 6.3. Tremor variables for PD patients who exhibited tremor on at least one of the tasks

ID	Rest				Circle Tracing				Spiral Tracing				UPDRS Tremor Score (Right hand)	
	OFF		ON		OFF		ON		OFF		ON		OFF	ON
	Freq	RP	Freq	RP	Freq	RP	Freq	RP	Freq	RP	Freq	RP		
PD002	n/a	n/a	n/a	n/a	6.8	46.8	n/a	n/a	6.9	30.5	n/a	n/a	0	0
PD004	n/a	n/a	n/a	n/a	6.3	70.3	n/a	n/a	6.5	63.9	n/a	n/a	0	0
PD007	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0	0
PD008	4.9	84.9	n/a	n/a	5.1	66.5	n/a	n/a	5.2	62.5	n/a	n/a	0	0
PD009	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	0	0
PD011	5.7	87.8	n/a	n/a	7.6	24.3	n/a	n/a	5.6	48.2	n/a	n/a	2	0
PD012	n/a	n/a	n/a	n/a	7.4	30.6	n/a	n/a	n/a	n/a	n/a	n/a	0	0
PD013	n/a	n/a	n/a	n/a	7.1	33.8	7.0	37.0	6.5	43.1	6.3	42.0	3	3

n/a = not available. If no value is available for the tremor measures, no tremor was detected during this task. Freq = Tremor (peak) frequency; RP = Relative Power.

## 6.5. Discussion

This study explored whether a set of graphical tasks could be used for monitoring PD by assessing its validity and response to dopaminergic medication. Moderate correlations between performance on graphical tasks and the PPT suggest that this set of graphical tasks is valid to assess and monitor upper limb function in PD patients. The advantage of using these graphical tasks, instead of, for instance, the PPT is that no examiner is needed, which makes the graphical tasks suitable for home-based monitoring.

Additionally, this study showed that this set of graphical tasks can be used to detect subtle changes, which are barely visible by observing the patient, in performance after taking medication in PD patients. We investigated the validity and response to dopaminergic medication of different measures of MT on graphical tasks to assess bradykinesia. Moderate correlations with the PPT score suggest that MT measures for the tracing tasks are valid for assessing and monitoring upper limb function in PD patients. In contrast, MT measures for the writing task showed only weak correlations with the PPT and seem to be less valid. FittsSlope, referring to the extent to which a patient becomes slower with increasing difficulty of Fitts' task, also correlated significantly with the PPT score, which means that FittsSlope can be used as a proper measure of bradykinesia. In agreement with previous studies regarding medication effects on performance of graphical tasks in PD<sup>[12,14,15]</sup>, MT on the writing task improved after taking medication (see Table 6.2). In addition, FittsSlope and MT on the simple circle and spiral tracing tasks also improved after taking medication in PD patients. Simple circle and spiral tracing tasks might be easier to perform correctly than a writing task in home-based settings without an examiner present. We also studied the validity and response to dopaminergic medication of different measures of tremor (presence or absence of tremor, tremor frequency and relative power around the tremor frequency) during the resting task and circle and spiral tracing tasks. The present study showed that tremor power generally decreased after medication intake in PD patients, which was reported previously as well<sup>[28]</sup>. Since tremor often is a prominent and disabling symptom of PD that may be influenced by treatment, a useful monitoring tool should include a measure to assess tremor. Previous studies investigating medication effects on graphical tasks did not include a measure to assess tremor<sup>[11,12,14,15]</sup>. Remarkably, MDS-UPDRS-III-tremor scores were 0 for almost all patients, although a tremor was detected during the graphical tasks. This suggests that graphical tasks might be more sensitive to detect a subtle tremor than the UPDRS. The difference in the

presence of tremor between the UPDRS and the graphical tasks could be explained by the fact that tremor scoring during the UPDRS involves observing movements of the upper limb different from the movements which are involved in the graphical tasks. For example, a clinician observes whether tremor is present during a simple flexion movement of the upper limb, whereas the graphical tasks require more complex movements of the upper limb. In addition, a tremor with a low amplitude and high frequency could be difficult to observe during a neurological assessment, while graphical tasks performed with a sensor pen could capture such tremors.

Besides bradykinesia and tremor, micrographia is a common symptom in PD patients<sup>[5,22,30]</sup>, which refers to a reduction in writing size and could be assessed quantitatively<sup>[5]</sup>. For screening PD, assessing micrographia has been shown to be useful, because differences were found between mildly affected PD and HC participants<sup>[31]</sup>. Our data showed that writing size measures correlated weakly with the PPT, suggesting that writing size, as assessed in this study, is not a valid measure to assess and monitor upper limb function in PD.

Additionally, writing size measures did not change after taking medication in PD patients, in agreement with previous studies that investigated writing size ON and OFF medication<sup>[11-13]</sup>. However, duration and size of writing are related<sup>[5,8]</sup>, so bradykinesia could compensate for micrographia. Therefore, micrographia assessments could be improved by writing a fixed number of letters or words in a particular time frame.

No significant correlations were found between performance on graphical tasks and the MDS-UPDRS-III-bradykinesia score. This could be explained by the fact that the MDS-UPDRS-III-bradykinesia items entail different movements of the arm and hand than graphical tasks and therefore involve other upper limb functions. Hand function of most PD patients in this study was only mildly affected, according to the MDS-UPDRS-III-bradykinesia subscore. Subtle improvements of hand function after taking medication were therefore hard to detect according to the MDS-UPDRS-III. In contrast, performance of almost all PD patients improved on graphical tasks after taking medication, which suggests that graphical tasks are more suitable to detect subtle changes in upper limb function than the MDS-UPDRS-III.

To use the current system as a home-based monitoring tool, the analysis methods should and could be converted to automatic methods, which generate simple outcome measures for the clinician. In addition, a home-based system should include a clear instruction manual for patients and error detection and feedback to ensure correct task execution and allow use of the system without an examiner present. Once the system is fully automated, a new study would be



needed to re-assess validity. To further investigate long-term disease progression and treatment effects, a longitudinal study should be performed in which PD patients will be followed for a longer time-period.

As a limitation, the medication effects in this study may have been influenced by a learning effect, because the measurements ON medication were performed approximately 1.5 hours after the measurements OFF medication. However, since the tasks were easy to perform and not all patients improved at the second measurement, it is assumed that this learning effect is not substantial. Another limitation of this study is that the resting task involved holding the pen-tip at a certain location, which makes it a postural rather than a resting task. Therefore this task is not suited to assess resting tremor. Since resting tremor is typical for PD patients, another resting task should be included in future studies that actually measures resting tremor. Furthermore, it would be interesting to assess the responsiveness of the graphical tasks. This could be done by comparing the change in performance on the graphical tasks with the clinically accepted change between ON and OFF medication. The clinically accepted change for PD patients would be a change in the UPDRS score. Since the patients in our study were only mildly affected and showed low UPDRS scores, a clear change in UPDRS was often not seen between ON and OFF medication. Therefore we did not compare the changes in graphical tasks to the small and often absent changes in UPDRS score, but only compared performance on the graphical tasks ON and OFF medication and pooled measurements ON and OFF medication to allow assessment of the validity of the graphical tasks.

## **6.6. Conclusions**

In conclusion, the present study showed that our set of graphical tasks using a digital tablet and sensor-pen is valid to assess and monitor upper limb functioning in PD patients, especially with respect to the circle, spiral and modified Fitts' task and their derived measures of MT and tremor. Our method is non-invasive, portable and can be used easily at home without an examiner, which offers great opportunities as an endpoint for future medication trials.

## 6.7. References

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