Graphical tasks to aid in diagnosing and monitoring Parkinson's disease
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CHAPTER 5

TREMOR PRESENCE AND MOVEMENT TIME MEASURES HELP IN DISTINGUISHING BETWEEN ESSENTIAL TREMOR AND PARKINSON’S DISEASE
5.1. Abstract

Clinical presentation of movement disorders, such as Parkinson’s disease and essential tremor, is complex and often variable. Therefore, correct diagnosis can be difficult. To aid in the clinical assessment of movement disorders, quantitative assessment of motor symptoms could be useful. A newly developed tool, consisting of a digital tablet and pen, could be used for this purpose. This tool records performance on graphical tasks, such as handwriting and drawing. In the present study we investigated whether this tool can also be used to differentiate between several tremor disorders. Patients with essential tremor (n=13), enhanced physiological tremor (n=10), functional tremor (n=8), tremor-dominant Parkinson’s disease (n=12), and healthy control participants (n=23) were included. They performed a set of graphical tasks, including figure tracing tasks, a writing task and a modified Fitts’ task. Gyroscope sensors in the pen were used to extract tremor characteristics, such as tremor frequency, power and amplitude. Movement time and writing size were calculated to assess other aspects of upper limb function. We showed that relative tremor power could be used to determine whether tremor was present during each of the tasks with high sensitivity and specificity (>0.8). We found that ‘tremor presence on four graphical tasks’ could be used to distinguish patients with essential tremor from other tremor patients with high sensitivity (1.00). Tremor amplitude was significantly lower in patients with enhanced physiological tremor compared to patients with essential tremor and functional tremor. Furthermore, Parkinson patients were generally slower on the graphical tasks than the other patients. Writing size did not differ between the groups. This study showed that our newly developed device, which is portable and non-invasive, can be used to detect tremor, with the advantage that multiple upper limb functions can be assessed simultaneously.
5.2. Introduction

Movement disorders, such as Parkinson's disease (PD) and essential tremor (ET), are common conditions, especially in the elderly. In general, the prevalence of PD is 1% and of ET 14% in people over 65 years [1]. The clinical presentation of movement disorders is complex and often variable [1]. Therefore, correct diagnosis can be difficult. For example, Jain et al. [2] reported that one out of three patients with essential tremor (ET) was misdiagnosed, based on clinical diagnosis by a non-movement disorders specialist. The most frequent false diagnosis of ET was Parkinson's disease. Especially if motor symptoms are not typical and show overlap between different movement disorders the clinical evaluation does not lead to a clear diagnosis. Additionally, clinical evaluation depends on the experience and interpretation of the physician. To aid in the clinical assessment of movement disorders, a method for quantitative assessment of motor symptoms could therefore be useful. An example of an objective motor assessment device is Kinesia (Great Lakes NeuroTechnologies, USA) [3,4]. The Kinesia system involves movement sensors that need to be worn on the index finger and has been used to assess upper limb function in patients with movement disorders [3–6]. Another tool which might be useful for objective assessment of motor symptoms employs a digital tablet and pen that can be used to perform and record graphical tasks, such as handwriting and drawing [7]. Previously, we used such a tool, which was newly developed in a European research project (‘DiPAR’, FP7-SME-201001 programme, grant agreement 262291) for the objective assessment of motor symptoms of PD patients [8]. We showed differences in performance on graphical tasks, employing this newly developed tool, between PD patients and HC participants [8]. Additionally, we showed that measures obtained with this tool were reproducible in healthy adults (Chapter 4 of this thesis) and we established the validity and the response to dopaminergic medication of these tasks (Chapter 6 of this thesis). In this chapter, we further explored the clinical possibilities of this newly developed tool by comparing performance on graphical tasks between patients with different movement disorders.

As mentioned before, PD and ET may show overlapping clinical presentations [2], particularly when a PD patient first presents with motor symptoms such as tremor. In addition, it can be difficult to clinically distinguish between ET or PD and other tremor syndromes, including enhanced physiological tremor (EPT) and functional tremor (FT). Therefore we focus on comparing PD, ET, EPT and FT patients in the present study. Tremor is defined
as a rhythmical, involuntary oscillatory movement of a body part\textsuperscript{9}, often the upper limb\textsuperscript{10}. Tremor can be classified as resting or action tremor\textsuperscript{11}. Resting tremor is one of the cardinal symptoms of Parkinson’s disease and occurs in a body part that is not voluntarily activated and is completely supported against gravity\textsuperscript{9}. ET, EPT and FT, however, are action tremors and occur with voluntary contraction of a muscle\textsuperscript{9}. Yet, ET patients could be wrongly diagnosed with PD, because early tremor-dominant PD patients can present only with tremor and advanced ET patients sometimes show a continuation of the tremor into the resting condition\textsuperscript{12}. In addition, ET, EPT and FT are all action tremors and have similar frequencies\textsuperscript{9,10}, which might render establishing the correct diagnosis difficult. In clinical settings a polymyography recording that provides specific characteristics of tremor can aid in differentiating between tremor disorders\textsuperscript{13,14}. For example, low tremor amplitude is often seen in EPT patients\textsuperscript{10} and entrainment or a change in tremor frequency with distraction is typical for FT patients\textsuperscript{15,16}. However, these tremor characteristics are not present in all patients, can be difficult to assess during a polymyography and are therefore not always helpful in correctly diagnosing a tremor patient. For this study we compared other measures of upper limb function between disorders in addition to traditional tremor characteristics.

An advantage of the newly developed tool, used in the present study, is that several aspects of upper limb function can be assessed simultaneously\textsuperscript{8}. The tool consist of a sensor-pen with a built-in gyroscope, which can be used to assess traditional tremor characteristics\textsuperscript{17,18}. Since the graphical tasks are performed with the sensor-pen, tremor characteristics can be obtained during all of these tasks. Importantly, pen-tip movements during the graphical tasks are recorded, which allows to derive movement time and writing size\textsuperscript{7,8}, measures which are related to the parkinsonian symptoms bradykinesia and micrographia\textsuperscript{19}. The graphical tasks consisted of circle, line and spiral drawing tasks and a writing task, because such tasks have been used previously to assess tremor characteristics and upper limb dysfunction of tremor patients\textsuperscript{7,8,20–26}. Additionally, a modified Fitts’ task was included to assess the speed-accuracy trade off\textsuperscript{27}, which might be impaired in patients with movement disorders\textsuperscript{28,29}.

To summarize, the aim of the present study was to explore whether a newly developed tool, consisting of a sensor-pen and digital tablet, can be used to differentiate between ET, EPT, FT and PD patients. Performance on several graphical tasks was recorded and analysed to assess differences in upper limb function between the groups.
5.3. Methods

5.3.1. Participants

The aim of this exploratory study was to include groups of ten patients with different upper limb tremor disorders. In addition, healthy control (HC) participants were included to define a cut-off value for the variable (see the next paragraph) which was used to determine whether participants had tremor or not during the graphical tasks. Patients with ET, EPT, FT and tremor-dominant PD (PDtd) were recruited from the University Medical Center in Groningen (UMCG) and the Martini Hospital (MH) in the Netherlands. In addition, 2 ET and 5 PDtd patients were added from another study in the European research project DiPAR, performed at the Dublin Neurological Institute (DNI) in Ireland. As inclusion criterion, all patients had a clinical diagnosis by a movement disorders specialist. PD patients were diagnosed according to the United Kingdom Parkinson’s Disease Society Brain Bank criteria\textsuperscript{[30]}. ET patients were diagnosed according to the criteria defined by the Tremor Investigation Group\textsuperscript{[31]}. Exclusion criteria for all participants were neurological or motor disorders other than they were included for, the use of medication affecting movement (other than for ET, EPT, FT or PDtd), or a low (< 26) score on the Mini Mental State Examination (MMSE), the latter to ensure understanding of task instructions. HC participants were recruited from the general population by advertisements and their average age was matched to the average age of the tremor groups. All participants were right-handed according to the Annett handedness scale\textsuperscript{[32]} and signed informed consent before participation. The study protocol was approved by the Medical Ethical Committee of the University Medical Center Groningen and the Medical Ethical Committee of the Dublin Neurological Institute.

5.3.2. 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, based on a concept by Manus Neurodynamica Ltd, were used. The pen contains a comprehensive integrated sensor and data acquisition system for highly accurate recordings. All recordings had a sampling frequency of 200 Hz. Position of the pen-tip on the tablet and gyroscope signals in three directions (pitch, yaw and roll) were analysed. The pen had a wireless connection to the tablet. Patients performed six 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. An example of incorrect task execution would be moving the pen in the wrong direction or starting the task before recording was started.

5.3.3. Tasks

Patients were instructed to start each task at a signal of the examiner. First, a recording of posture (30 seconds) was performed. Patients were seated with the 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 centre of the tablet. Subsequently, the patients traced circle, spiral and zigzag figures which were displayed on the tablet (see Figure 5.1). 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. The next task consisted of writing ‘elelelel’ five times with each phrase starting at the left side of the tablet, once with visual feedback (WFB) and once without visual feedback (NFB). An example was provided on paper on the table above the tablet. Next, a modified Fitts’ task was performed, which was similar to Fitts’ original task[27] and 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).
Figure 5.1. Templates and their dimensions for the tracing tasks: a circle, spiral and zigzag figure.

5.3.4. Data analysis

The recorded data were analysed to assess different aspects of upper limb function. Spectral analysis was used to analyse tremor presence and tremor characteristics. In addition, movement time during the tracing and writing tasks, writing size during the ‘elelelel’ task, and speed/accuracy trade-off during Fitts’ task were investigated.

Tremor analysis

For the posture, circle, spiral and zigzag tasks, the gyroscope signals were pre-processed and analysed to assess the tremor characteristics peak frequency (PF), relative power around the peak frequency (RP), and tremor amplitude (TA) (see Appendix 4). These calculations were automatically applied to all data, so that for all participants PF, RP and TA were determined for the posture, circle, spiral and zigzag tasks, even if a patient did not exhibit tremor. Presence of tremor can be variable in tremor patients and certain tasks might be more influenced by
tremor than others\textsuperscript{[10]}. It was therefore expected that tremor presence could also be variable across the tasks used in this study. For that reason, we subsequently determined whether tremor was present during each of the tasks for all participants by inspecting the power spectral density plots (PSD, see Appendix 4) for all tasks and participants, individually. We verified by visual inspection whether a clear peak between 4 and 12 Hz (frequency range for the different tremor disorders\textsuperscript{[10,33]}) was present in the plot. This procedure resulted in a binary variable, where a score of 1 indicated that a tremor peak was present in the PSD plot and a score of 0 that no tremor peak was present in the PSD plot. A more objective measure for the absence of tremor would be a low value for RP\textsuperscript{[34]}. However, this requires a cut-off value for RP which is unknown a-priori. For future reference, we therefore determined such a cut-off value on the basis of the visual inspection results. Based on the binary variable, a cutoff value for RP was determined for the posture, circle, spiral and zigzag task separately, using receiver-operator-curve (ROC) analyses in SPSS (IBM SPSS Statistics 22). The cut-off values were chosen such that they resulted in the highest area under the ROC. Furthermore, for each participant who showed tremor on at least one of the tasks, the number of tasks on which they showed tremor was determined. Finally, TA was compared between patients with different types of tremor who showed tremor on at least one of the tasks.

Other motor control features
Mean movement time (MT) per trial was calculated for the tracing tasks (CircleMT; SpiralMT and ZigzagMT). The data of the ‘elel’ task were preprocessed to evaluate characteristics of each separate letter (see Appendix 2). For both conditions of the ‘elel’ task mean MT for each letter was calculated (E_MT(WFB), E_MT(NFB), L_MT(WFB) and L_MT(NFB)), as well as mean width and height (E_Width(WFB); E_Height(WFB); L_Width(WFB); L_Height(WFB); E_Width(NFB); E_Height(NFB); L_Width(NFB); L_Height(NFB)). The modified Fitts’ task was analysed according to Fitts’ law (Fitts, 1954) (see Appendix 5), yielding the measures FittsSlope and FittsR2. FittsSlope represents the extent to which performance becomes slower with an increase in difficulty of the task and FittsR2 represents the degree of compliance with Fitts’ law.

Statistical analysis
Statistical analyses were conducted using SPSS (IBM SPSS Statistics 22). First, normality of features was assessed by the Shapiro-Wilk test. For all groups, features were described by their mean and standard deviation (sd) when
Differences between Tremor Disorders

normally distributed, or median and interquartile range (IQR), when not normally distributed. The goal of this study was to investigate whether features derived from tracing, drawing and other fine motor control tasks differed between the tremor disorders and HC. For the features which were normally distributed a one-way ANOVA with post-hoc testing when appropriate (Bonferroni-corrected for multiple comparisons) was used to test for differences between groups. Otherwise a Kruskall-Wallis test was used to test whether groups differed and separate Mann-Whitney U tests were used for post-hoc testing when appropriate. Width and height of the ‘e’ and ‘l’ were compared between the two conditions of the ‘elelelel’ task according to a repeated measures ANOVA with between-subjects factor ‘Group’ (5 groups: ET, EPT, FT, PD and HC) and within-subjects factor ‘Feedback’ (2 levels: with and without feedback), since micrographia has been found to improve in PD patients when writing without visual feedback[35].

5.4. Results

In total 66 participants completed all tasks (Table 5.1). The participants were divided in five groups: ET (n=13), EPT (n=10), FT (n=8), PDtd (n=12) and HC (n=23). For some of the ET, EPT and FT patients a polymyography report was available. Information on traditional tremor characteristics was extracted from these files and, if available, from the clinical patient file. The patient characteristics are summarized in Table 5.1. For 7 of the 12 PDtd patients a UPDRS-III-motor score was available which ranged from 10–42. The UPDRS-tremor sub score ranged from 0–4 for these PDtd patients. There was a difference in age across groups (F(4,61)=3.5; p=0.01); EPT patients were younger than ET (p=0.04) and PDtd patients (p=0.001). For one ET patient, data were missing for the modified Fitts’ task due to a technical problem, so this patient was excluded from further analysis of this task.
### Table 5.1. Participant characteristics

<table>
<thead>
<tr>
<th></th>
<th>ET</th>
<th>EPT</th>
<th>FT</th>
<th>PDtd</th>
<th>HC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>13</td>
<td>10</td>
<td>8</td>
<td>12</td>
<td>23</td>
</tr>
<tr>
<td>Male/Female</td>
<td>9/4</td>
<td>4/6</td>
<td>2/6</td>
<td>5/7</td>
<td>15/8</td>
</tr>
<tr>
<td>Age in years (mean(range))</td>
<td>60 (34–81)</td>
<td>42 (21–75)</td>
<td>59 (27–76)</td>
<td>68 (49–88)</td>
<td>53 (30–75)</td>
</tr>
<tr>
<td>Years since diagnosis (mean(range))</td>
<td>32 (5–60)</td>
<td>10 (1–25)</td>
<td>13 (0.5–40)</td>
<td>5 (1–10)</td>
<td>na</td>
</tr>
<tr>
<td>Polymyography (present/not present)</td>
<td>3/10</td>
<td>8/2</td>
<td>6/2</td>
<td>0/12</td>
<td>na</td>
</tr>
<tr>
<td>High frequency tremor (8–12 Hz)*</td>
<td>na</td>
<td>6</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Frequency change upon loading*</td>
<td>na</td>
<td>7</td>
<td>na</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Low amplitude*</td>
<td>na</td>
<td>2</td>
<td>6</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Variable frequency*</td>
<td>na</td>
<td>na</td>
<td>7</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Change in tremor freq when distracted*</td>
<td>na</td>
<td>na</td>
<td>3</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Entrainment*</td>
<td>na</td>
<td>na</td>
<td>3</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Postural tremor*</td>
<td>7</td>
<td>9</td>
<td>6</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Action tremor*</td>
<td>7</td>
<td>2</td>
<td>3</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Intention tremor*</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Resting tremor*</td>
<td>na</td>
<td>na</td>
<td>4</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td>Medication for tremor</td>
<td>no</td>
<td>no</td>
<td>yes**</td>
<td>no</td>
<td>na</td>
</tr>
<tr>
<td>Time since last medication (hours)</td>
<td>na</td>
<td>na</td>
<td>na</td>
<td>0.5–5</td>
<td>na</td>
</tr>
</tbody>
</table>

N=number of participants; ET=Essential tremor; FT=Functional tremor; EPT=Enhanced Physiological tremor; PDtd=tremor-dominant Parkinson’s disease; HC=Healthy Control participants; UPDRS=Unified Parkinson’s Disease Rating Scale; na=not applicable. *Number of patients who showed the characteristic are displayed. The clinical patient file and polymyography report, if available, were used to determine the presence of these characteristics. **11 PDtd patients used dopaminergic medication and for 1 PDtd patient medication use was unknown.

#### 5.4.1. Tremor analysis

Visual inspection of the PSD plots revealed that 40 of the 66 participants exhibited tremor on at least one of the tasks. During the posture task 28 participants exhibited tremor and during the circle, spiral and zigzag task 31, 32 and 30 participants exhibited tremor, respectively. We investigated whether a high value of RP could be used to indicate the presence of tremor. Based on the results of the visual inspection, the following cut-off values for RP were determined by ROC analysis; posture task: RP=23.7, circle task: RP=31.4, spiral task: RP=31.8, and for the zigzag task: RP=30.8. A score above these cut-off values would mean that tremor is present during the task and a score below the cut-off would indicate the absence of tremor during the task. Using the established optimal cut-off values, the presence of tremor was detected with a sensitivity of 0.96 and a specificity of 0.97 for the posture task, for the circle task with a sensitivity of 0.87 and a specificity of 0.91, for the spiral task with a sensitivity of 0.88 and a specificity of 0.91, and for the zigzag task with a sensitivity of 0.73 and a specificity of 0.81. For each of the patients who exhibited tremor on at least one of the tasks the TF, RP, and TA were averaged over the
tasks on which they exhibited tremor. These mean values were compared between the groups (see Table 5.2). A one-way ANOVA showed that TF and RP were significantly different between the groups (F(4,35)=4.0 for TF and 4.3 for RP, p<0.01). TF was significantly higher in EPT patients compared to ET patients (p=0.04), and PDtd patients (p=0.02), and RP was significantly higher in ET compared to EPT (p=0.009) patients. A Kruskall-Wallis test showed that TA was also significantly different between the groups (Chi square(4)=19.1, p=0.001, see Figure 5.2). Post-hoc Mann Whitney U tests showed that TA was significantly lower in EPT patients compared to ET patients (p=0.001) and FT patients (p=0.002), and significantly lower in HC participants compared to ET patients (p=0.002). We observed that all 12 ET patients who showed tremor during at least one of the tasks, exhibited tremor on all four tasks. Therefore, the variable ‘showing tremor on four tasks’, allows to distinguish ET patients from other tremor patients, with high sensitivity (1.00), but lower specificity (0.57). Additional details about the results of the tremor analysis, are illustrated in Figure 5.3.

Table 5.2. Tremor characteristics

<table>
<thead>
<tr>
<th>Tremor presence</th>
<th>TF(mean(sd))</th>
<th>RP(mean(sd))</th>
<th>TA (mean(sd))</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 task (n)a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ET (n=13)</td>
<td>12</td>
<td>12</td>
<td>6.3 (1.2)</td>
</tr>
<tr>
<td>EPT (n=10)</td>
<td>10</td>
<td>4</td>
<td>8.0 (1.4)c</td>
</tr>
<tr>
<td>FT(n=8)</td>
<td>7</td>
<td>5</td>
<td>6.5 (1.0)d</td>
</tr>
<tr>
<td>PDtd(n=12)</td>
<td>6</td>
<td>3</td>
<td>5.9 (1.0)</td>
</tr>
<tr>
<td>HC(n=23)</td>
<td>5</td>
<td>0</td>
<td>7.4 (1.9)</td>
</tr>
<tr>
<td>4 tasks (n)b</td>
<td>60.0 (15.5)</td>
<td>33.4 (12.8)d</td>
<td>0.31 (0.29)</td>
</tr>
<tr>
<td>12</td>
<td>34.4 (15.1)</td>
<td>0.08 (0.03)e</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>36.7 (9.1)</td>
<td>0.15 (0.14)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10.0 (0.02)</td>
<td>0.10 (0.02)</td>
<td></td>
</tr>
</tbody>
</table>

a) The number of patients for each group who exhibited tremor on at least one of the graphical tasks (Posture task, circle tracing task, spiral tracing task, zigzag tracing task). b) The number of patients for each group who exhibited tremor on all four graphical tasks. c) Significantly different from ET and PDtd, at α=0.05. d) Significantly different from ET, at α=0.01. e) Significantly different from ET an FT, at α=0.01. f) Significantly different from HC, at α=0.01. # for these groups TA was not normally distributed, so median (interquartile range) is shown.
Figure 5.2. Boxplot of tremor amplitude (TA, in angular degrees) for each of the groups. TA was averaged over all graphical tasks: Posture and circle, spiral, zigzag tracing. Only patients who exhibited tremor on at least one of the tasks are included. Significant differences are shown in the graph (* significant at $\alpha=0.01$). ET=Essential Tremor, EPT=Enhanced Physiological Tremor, FT=Functional Tremor, PDtd=Tremor-dominant Parkinson’s disease, HC=Healthy controls.
DIFFERENCES BETWEEN TREMOR DISORDERS

5.4.2. Other motor control features

Movement time (MT) for the circle, spiral, zigzag and ‘elelelel’ tasks was significantly different between groups (Kruskall-Wallis, all p<0.05, see Table 5.2). Post-hoc Mann Whitney U tests showed that MT was significantly higher in PD patients compared to ET patients for all drawing and writing tasks (all p<0.05) and compared to EPT patients only for the circle tracing task (p=0.02). MT on the circle tracing task was also significantly higher in FT patients compared to ET patients (p=0.04). The duration of writing an ‘e’ in both ‘elelelel’ tasks was significantly higher in PD patients compared to FT patients (p=0.03...
and \( p=0.01 \). The duration of writing an ‘\( e \)’ in the ‘elelelel’ task without feedback was significantly higher in EPT patients compared to FT patients (\( p=0.04 \)). Since PD patients on average had the highest MT on the tracing tasks, we used ROC analyses to investigate whether PD could be distinguished from the other groups based on MT measures. A cut-off value for CircleMT of 4.7 s, showed that PD patients could be distinguished from the other patients with a sensitivity of 0.83 and a specificity of 0.70. There were no significant differences in writing size for the ‘elelelel’ task between any of the groups. For all groups writing size of the ‘elelelel’ task was significantly higher in the NFB condition compared to the WFB condition (all \( p<0.001 \)). Only L_Width showed a significant interaction effect for group and feedback (\( F=2.7; p=0.04 \)).

Table 5.3. Descriptives for movement time features for each of the groups. Median (iqr) values are displayed, because the features were not normally distributed.

<table>
<thead>
<tr>
<th>Feature</th>
<th>ET</th>
<th>EPT</th>
<th>FT</th>
<th>PDtd</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CircleMT*</td>
<td>3.1 (2.3)</td>
<td>3.9 (1.4)</td>
<td>5.4 (2.8)</td>
<td>5.9 (1.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>SpiralMT*</td>
<td>9.7 (6.6)</td>
<td>10.3 (5.9)</td>
<td>12.1 (5.6)</td>
<td>15.7 (8.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>ZigzagMT*</td>
<td>8.4 (6.4)</td>
<td>13.2 (4.6)</td>
<td>10.9 (8.0)</td>
<td>15.2 (13.2)</td>
<td>0.006</td>
</tr>
<tr>
<td>EMT (WFB)*</td>
<td>0.3 (0.1)</td>
<td>0.5 (0.2)</td>
<td>0.4 (0.2)</td>
<td>0.5 (0.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>LMT (WFB)*</td>
<td>0.4 (0.1)</td>
<td>0.6 (0.1)</td>
<td>0.5 (0.2)</td>
<td>0.7 (0.6)</td>
<td>0.004</td>
</tr>
<tr>
<td>EMT (NFB)*</td>
<td>0.4 (0.1)</td>
<td>0.5 (0.2)</td>
<td>0.3 (0.1)</td>
<td>0.5 (0.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>LMT (NFB)*</td>
<td>0.5 (0.2)</td>
<td>0.7 (0.1)</td>
<td>0.6 (0.2)</td>
<td>0.8 (0.6)</td>
<td>0.007</td>
</tr>
<tr>
<td>FittsSlope*</td>
<td>0.1 (0.1)</td>
<td>0.1 (0.0)</td>
<td>0.1 (0.1)</td>
<td>0.2 (0.1)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

ET=Essential tremor; EPT=Enhanced Physiological tremor; FT=Functional tremor; PDtd=tremor-dominant Parkinson’ disease; HC=Healthy control participants, iqr=inter quartile range. *A Kruskall-Wallis test was used to investigate whether there was a difference between the four groups, p-values are shown in this table.  
a) Significant difference between PD and ET, at \( \alpha=0.05 \). b) Significant difference between PD and EPT, at \( \alpha=0.05 \). c) Significant difference between PD and FT, at \( \alpha=0.05 \). d) Significant difference between ET and FT, at \( \alpha=0.05 \). e) Significant difference between EPT and FT, at \( \alpha=0.05 \).

5.5. Discussion

The aim of this study was to explore whether a newly developed tool, consisting of a sensor-pen and digital tablet, can be used to differentiate between ET, EPT, FT and PD patients. The strength of this study is that four tremor disorders were included and that multiple upper limb functions, in addition to traditional tremor characteristics, were assessed. Tremor presence on all four graphical tasks seems a useful variable to distinguish ET patients from the other tremor disorders. Tremor amplitude might be useful to distinguish EPT patients from other tremor patients. Movement time on all graphical tasks differed between PD and ET patients and might be useful to distinguish PD from other tremor patients.
First, we showed that relative power (RP) around the peak frequency (PF) could be used to determine whether tremor was present during each of the tasks, with high sensitivity (0.73 – 0.96) and specificity (0.80 – 0.97). Since the sensitivity and specificity were the lowest for the zigzag task, we suggest that RP on the zigzag task is less suitable to determine whether tremor is present than RP on the posture, circle and spiral tasks. Previously, graphical tasks, similar to our posture, circle and spiral tasks have been used to assess tremor, as well\[12,17,20–22,34,36\]. Interestingly, we found that almost all ET patients showed tremor on at least one of the tasks, and all of these ET patients showed tremor on all four tasks. ‘Showing tremor on all four tasks’ could thus be used in this study to distinguish ET patients from other tremor patients with high sensitivity (1.00). In the EPT, FT and PD group only a few patients showed tremor on all four tasks (see Table 5.2 and Figure 5.3).

Secondly, our results regarding traditional tremor characteristics were similar to results in previous literature. In agreement with van der Stouwe et al.\[41\], tremor frequency was significantly higher in the EPT group compared to the ET and PD groups. However, individual tremor frequencies were too much overlapping, so this variable could not be used to clearly distinguish EPT from other tremor patients. In line with previous literature\[10,11\], tremor amplitude was significantly lower in the EPT group, especially compared to the ET and FT groups. However, some ET and FT patients also showed low tremor amplitude, so we could not determine a cut-off value for tremor amplitude to distinguish EPT patients from the other tremor patients with high sensitivity and specificity. Hence, tremor amplitude might be used, but only in combination with other performance measures, to distinguish EPT from other tremor disorders.

Besides tremor characteristics, we investigated differences in other aspects of upper limb function between ET, EPT, FT and PD patients. As expected, PD patients generally performed the tasks slower than the other patients and these differences were significant when comparing PD patients to ET patients (see Table 5.3). Since the most common misdiagnosis of ET is PD\[2\], we suggest that MT on drawing tasks should be taken into account when assessing a possible ET patient. As expected, performance on the modified Fitts’ task was most impaired in PD patients\[28,29\]. Especially the extent to which the movement became slower with an increase in difficulty (FittsSlope) was significantly higher in PD patients compared to EPT patients. No further differences were found between the tremor groups based on the modified Fitts’ task in this study. The modified Fitts’ task could be improved in future studies\[37\], for example, by (considerably) increasing the distance between the targets to allow investigation of intention tremor. Intention tremor is common in ET patients\[38,39\] and is
defined as an increase in tremor amplitude toward the termination of a visually guided goal-directed movement. Analysis of intention tremor during a modified Fitts’ task might therefore be helpful to distinguish ET from other tremor patients.

Another aspect of upper limb function which could be impaired in tremor patients and is easy to assess with a digital tablet and a sensor-pen, is the size of writing. Reduction in writing size is a symptom called micrographia which is often found in PD patients. In this study, we did not find significant differences in writing size between the groups. This could be explained by the fact that PD patients do not always suffer from micrographia. In addition, the surface of the tablet is smoother than normal paper, which could make it easier for patients to write. Remarkably, all groups, not just the PD patients, showed a significant increase in writing size when writing without visual feedback compared to writing with visual feedback. Previously, this phenomenon has, to our knowledge, not been investigated in other tremor groups. Our results suggest that this effect cannot be used to distinguish between different tremor disorders.

Furthermore, we did not find clear differences in upper limb function between FT patients and other tremor patients. This might be due to the fact that FT patients may have various clinical presentations. Future studies could include a distraction or entrainment task. Distractibility and entrainment tests have been shown to have high sensitivity and specificity to clinically assess FT. Besides investigating characteristics for FT, van der Stouwe et al. also investigated specific characteristics to identify EPT patients. They described that change in tremor frequency upon loading of the tremulous arm was specific for EPT. Loading of the tremulous arm while performing the graphical tasks might therefore help to distinguish EPT from other tremor disorders.

One of the limitations of this study is that only a small number of patients was included in each group, which limits power. Especially after identifying the patients who had tremor during the tasks, only a few patients remained in each group. Despite these small groups, we observed interesting differences in, for example tremor amplitude or the number of tasks during which tremor was present. These findings should be further investigated in larger groups. Another limitation in the experimental set-up used in this study is that no resting task was included. Resting tremor is a cardinal symptom of PD and could therefore further improve distinguishing between PD and other tremor disorders. A resting task should thus be included in future studies and could, for example, be similar to the posture task, but without touching the tablet with the pen-tip.
5.6. Conclusions

This study showed that our newly developed device, which is portable and non-invasive, can be used to detect tremor, with the advantage that multiple upper limb functions can be assessed simultaneously. Differences in performance on graphical tasks were found between tremor disorders, however these differences should be confirmed in larger studies. Based on the results of this study we recommend using more than one graphical task when assessing tremor patients, since the presence of tremor can be variable. Showing tremor on all tasks could then be used as a variable to identify ET patients. Low tremor amplitude is suggested to be most useful to identify EPT patients. Movement time on simple drawing and writing tasks, in addition to tremor characteristics, seems the most suitable measures to distinguish PD from ET patients.

5.7. References


[41] Van der Stouwe, A. M. M. Diagnosis and Imaging of Essential and other Tremors (PhD thesis), (University of Groningen, University Medical Center Groningen, the Netherlands, 2015).