Graphical tasks to aid in diagnosing and monitoring Parkinson's disease
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CHAPTER 2

THE DiPAR PROJECT
2.1. Introduction

The experimental studies described in this thesis were performed as part of the European research project, titled ‘DiPAR’ (‘Diagnosing Parkinson’s Disease by neuromuscular function evaluation’). The aim of the DiPAR project was to develop and evaluate a novel tool for the early identification, confirming of diagnosis and monitoring of Parkinson’s disease (PD), based on a concept by Manus Neurodynamica Ltd (Manus). Manus is a high tech enterprise, based in England that instigated and led the project in which eight partners collaborated. The project received funding under the European 7th Framework programme (Grant Agreement 262291). UMCG was invited into the consortium to support the development and validation of clinical assessment of motor symptoms with the DiPAR system. This chapter provides a more detailed overview of the DiPAR project.

2.2. Background

Zietsma[1], owner of Manus, described in his PhD thesis the development of a comprehensive system for investigation of biomechanical and neuromuscular processes involved in handwriting and drawing within the context of unanswered questions on neuromotor control in healthy individuals and those with impaired motor function. Based on understanding of research questions in the field, along with new upcoming technologies, such as more accurate and miniaturized motion sensors and various types of writing tablets as well as demands of the healthcare systems, Zietsma recognized an opportunity to continue his work. In 2008, backed by commercial funding, a proof of concept project was started to develop a second system for handwriting analysis that could help to improve understanding of PD and that may be implemented in PD management. The proof of concept was successful and two prototypes were delivered and the concept was patented in 2010. In the DiPAR project the research and development (R&D) was continued.

2.2.1. DiPAR collaborators

Manus composed a consortium for the implementation of the research in the DiPAR project in 2009. The consortium consisted of the following Research and Technology Development (RTD) performers and the small and medium-sized enterprises (SMEs):
2.2.2. Role of each partner

Partners Manus, Inotec and Fraunhofer took responsibility for developing, testing and improving the hardware and the data acquisition software of the DiPAR system. The novel tool was evaluated and tested in several experimental studies, by researchers from the UMCG. Taking the lead in designing the experimental studies, designing the set of standardized graphical tasks and executing the experimental studies, UMCG was responsible for requesting medical ethical approval, recruitment of the relevant patient groups and data collection. UMCG also performed data analysis in cooperation with VTT and was responsible for the statistical analyses regarding group differences. The main results of these experimental studies and analyses are provided in Chapters 3–6 of this thesis. The role of each of the other partners is shortly mentioned in the following paragraph.

VTT was involved in the data analysis, together with UMCG and was also responsible for developing signal processing techniques to extract useful features from the raw data. Additionally, they were involved in developing automatic classification algorithms. The University of Glasgow was responsible for developing a patient data communication platform for the secured transmission of the data to a centralized database, which was hosted by the University of Glasgow. This platform was intended to be used as a ‘live’ platform to be managed by partner Hispafuentes for Manus, where recorded data during measurements should be transmitted to a data processing centre to analyse the data. This process should result in an easy interpretable outcome measure for health care workers. Manus, as lead partner, also facilitated the R&D to enable integration of the various hardware and software components developed by the other partners and took the lead in the exploitation and dissemination of the
project activities. In addition, Manus was responsible for finance, consortium and project management with support from partners Hispafuentes and Fraunhofer.

2.3. The DiPAR prototype systems

The DiPAR system was used to perform and record graphical tasks, such as handwriting and drawing. The DiPAR system consists of a hand-held device (the DiPAR-pen), a digital tablet and an operator computer. Signals are recorded during the graphical tasks, such as pen displacement and pen grip force. A patent is associated with the pen (patent WO/2011/141734: Apparatus for use in diagnosing and/or treating a neurological disorder). For the DiPAR project different progressive prototypes were used. The first prototype of the pen (V1) had a wired connection to a writing-tablet. This prototype recorded pen-tip displacement and pen-grip force and was used for the first experimental study described in Chapter 3 of this thesis. The second prototype (V2) was re-designed by partner Fraunhofer, based on recommendations resulting from earlier designs and studies. This prototype consisted of a sensor-pen (the DiPAR-pen), that incorporated accelerometers and gyroscopes, with a wired connection to a digital tablet (ASUS Eee Slate EP121). With this prototype pen-tip displacement and pressure, pen-grip force, acceleration and gyration (both in three dimensions) were recorded. The V2 prototype was used for the experimental studies described in Chapter 4 and 5 of this thesis. The third and final prototype in the DiPAR project (V3) recorded the same signals as V2, but the pen-tablet connection was now wireless and the pen had improved grips to hold it. The V3 prototype was used for the experimental study described in Chapter 6 of this thesis. In summary, the following prototypes were used within the DiPAR project (Figure 2.1):

V1. DiPAR Prototype I: recording pen-tip displacement and pen-grip force

V2. DiPAR Prototype II: recording pen-tip displacement and pressure, pen-grip force, accelerometer and gyroscope signals

V3. DiPAR Prototype III: similar to V2, but with a wireless pen-computer connection.
Figure 2.1. The different prototypes of the DiPAR system. The photos in row A represent prototype V1, the photos in row B prototype V2 and the photos in row C prototype V3.

The V2 and V3 DiPAR pens thus contain a comprehensive integrated sensor and data acquisition system for highly accurate recordings of graphical tasks, such as handwriting and drawing. All signals were recorded at a sampling frequency of 200 Hz, and were synchronized and saved in one ‘logfile’ allowing easy and reliable analysis of the data. The raw data in the logfiles can be used to develop algorithms to analyse the data. Within the DiPAR project, an algorithm was developed by VTT, which uses the logfiles as input and provides many features, including movement time and writing size. These features are ready to be used in research projects to perform statistical analyses. Further, the developed software enables the examiner to control the tablet from another operator computer or laptop. The operator software can be installed easily on a desktop computer or laptop. Using this software the examiner also verifies whether the sensor-pen has a proper connection to the tablet to ensure that data is actually recorded and logfiles are created. Since the V3 pen is wireless, the pen needs to be charged in a charging station. It takes about an hour for the pen to be fully charged. When the pen is fully charged, it can be used actively for about an hour, which is sufficient to perform all tasks in the task battery. Although the wired pen can generally be handled well, the wireless pen is more comfortable and much easier to handle. The pen-grips to hold the pen were improved during the project. The V3 prototype has symmetrically distributed pen-grips for the index finger, middle finger and thumb, which makes the pen easy to hold correctly.
Furthermore, the digital tablet allows easy and quick uploading of new templates which can be used for the graphical tasks. The final, V3, prototype is thus very suitable for research purposes, because it is portable, easy to use and provides synchronized data. Researchers can choose to work with the raw data or use the features which are provided by the developed algorithm.

### 2.4. **Experimental studies**

The DiPAR system was tested and evaluated in the experimental studies, which are described in Chapters 3–6 of this thesis. In Chapter 1 an outline of each of the chapters was provided. To summarize, the following prototypes of the DiPAR system were used for the experimental studies, described in the chapters of this thesis:

- **Chapter 3: PD vs HC** Prototype V1
- **Chapter 4: Reproducibility in healthy adults** Prototype V2
- **Chapter 5: Differences between tremor disorders** Prototype V2
- **Chapter 6: PD OFF vs ON medication** Prototype V3

In addition to the experimental studies described in this thesis, some other studies were performed within the DiPAR project to test and evaluate the DiPAR system. To get a first impression of the performance of the DiPAR system in a real clinical setting, a prospective study was performed. This study was performed with prototype V2. Unselected patients visiting the movement disorders outpatient clinic of a tertiary referral centre executed the graphical tasks with the DiPAR-pen. This study was performed to investigate whether PD patients could be distinguished from patients with other MD, based on the definite diagnosis, which was obtained later from the patient file. This study was performed at the Dublin Neurological Institute (DNI) in Ireland and at the UMCG. At the DNI 39 patients were included and at the UMCG 40 patients were included.

Additionally, the DiPAR system might be useful as an aid in the diagnostic process, by distinguishing PD patients from patients with other MD resulting in Parkinsonian symptoms. For example, dystonia may results in Parkinsonian symptoms and could therefore enter the differential diagnosis of a PD patients[2]. For that reason a few dystonia patients (writer’s cramp, n=8) from the Academic Medical Center (AMC) in Amsterdam were asked to perform the graphical tasks with the DiPAR-pen.

Furthermore, the experiments described in Chapter 3 and a part of the experiments described in Chapter 5 included the recording of muscle activity,
using surface electromyography (EMG) measurements. During the graphical tasks, performed with the DiPAR-pen, EMG signals were obtained from eight muscles of the right upper limb, which were expected to be active during such graphical tasks (Extensor Carpi Radialis Brevis, Extensor Carpi Ulnaris, Flexor Carpi Radialis, Biceps Brachii Longus, Triceps Brachii Medialis, Deltoides Anterior/Medialis/Posterior). EMG signals were recorded to allow comparison of EMG measures for rigidity\cite{3,4} with features derived from the DiPAR system.

Besides testing the DiPAR system in different patient groups, the experiments within the DiPAR project were also used to acquire knowledge on usability of the DiPAR-pen for patients with MD, and on usability of the DiPAR system from the examiner’s point of view. For example, we interviewed participants to find out whether the size and weight of the pen was acceptable allowing them to hold the pen correctly to perform several graphical tasks in a row. Additionally, we noted the time necessary to set-up the experiment and the time it took for patients to complete all tasks.

The usability results, as well as the results of the EMG study, the prospective study and the dystonia patients are not reported in this thesis. However, in Chapter 7 we will shortly discuss our experiences with the DiPAR system (hardware and software related) during the DiPAR project and give some recommendations for improvement of the DiPAR system for (future) clinical applications.

### 2.5. Task selection

At the start of the DiPAR project, the UMCG, in collaboration with partners Manus and VTT, designed the graphical tasks used in the experiments based on previous literature, as described in Chapter 1. During the DiPAR project the graphical tasks were evaluated and discussed and some tasks were added or removed from the experimental set-up between the different studies. Each of the Chapters 3–6 of this thesis provides a more extensive description and background of the set of tasks used in that chapter. Using the main findings of previous literature (see section 1.3.4) the following graphical tasks were designed during the DiPAR project:

- Tracing and drawing figures: a circle, a spiral, lines (in a star and zigzag figure, see Figure 2.2)
- Handwriting: ‘elelelel’ writing and a complete (Dutch) sentence (see Figure 2.2)
In addition, some other tasks were designed during the DiPAR project. Firstly, a resting task was designed to assess resting tremor, since this is one of the cardinal signs of PD\cite{5}. In this task, the participant was seated in front of a table with the elbow resting on the table and the pen-tip touching the tablet. Secondly, a ‘diadochokinesis’ task was designed. One of the tasks which is clinically used to assess bradykinesia is the ‘diadochokinesis’ task. In this task the patient performs rapid alternating movements of the wrist (pronation and supination). In the experimental set-up of the DiPAR project a similar task was included. The patients performed the diadochokinesis task while holding the pen. Thirdly, a modified Fitts’ task was designed in the DiPAR project after the first experimental study (Chapter 3). Fitts\cite{6} described that movement time varied systematically with changes in movement amplitude and target width (when accuracy was held constant). Performing smaller movements or movements to a larger target are easier and therefore performed more rapidly. This relationship is currently known as ‘Fitts’ law’. Previous literature showed that there are differences in performance on a Fitts’ task between PD patients and HC participants\cite{7–9}. In general, PD patients had difficulty in producing larger movements (for a constant target size) and movements to smaller targets (when the distance between targets was held constant). The original Fitts’ task was adapted to the size of the digital tablet which was used in the DiPAR project.

Furthermore, some of the drawing and handwriting tasks were extended by adding an extra condition. Previous studies regarding micrographia in PD showed that micrographia was expressed more strongly in PD patients during tasks with visual feedback of their handwriting\cite{10,11}. To investigate this phenomenon in the DiPAR project, the writing and zigzag drawing tasks were performed with and without online feedback on the screen of the digital tablet. These tasks were only included in the experimental studies which were performed with the V2 and V3 prototypes, since those prototypes incorporated a digital tablet which could provide visual feedback on the screen during writing. In the V1 prototype a writing tablet was used which could not provide visual feedback during writing. Besides the zigzag task being performed with and without feedback, one more condition was added to the zigzag drawing task. This condition consisted of drawing the zigzag figure vertically, while the zigzag figure template was presented horizontally on paper above the tablet. This task was added, because de Jong et al.\cite{10} observed that PD patients had difficulty drawing a zigzag figure in a different orientation than the presented example of the zigzag figure.
During the DiPAR project the tasks were evaluated and tested regarding their usability in finding differences in performance between PD patients and patients with other MD. In addition, during the experiments we could observe whether the instructions of the tasks were easy to understand by participants and whether participants were able to perform the tasks correctly with the DiPAR-pen. Since the time in the DiPAR project was limited, not all results of all tasks have been analysed. To summarize, the following graphical tasks were used within the DiPAR project (Figure 2.2 provides the templates of the tasks):

- Resting task (with the pen-tip touching the tablet)
- Diadochokinesis task (while holding the pen)
- Circle tracing
- Spiral tracing
- Line tracing in different directions (Star tracing)
- Zigzag tracing and drawing (with and without feedback, and rotated)
- ‘elelelel’ writing (with and without feedback)
- Modified Fitts’ task (eight subtasks)
- Sentence writing (Dutch sentence: ‘Veel te veel felle schelle zon’)

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Figure 2.2. The templates of the graphical tasks which were mainly used in the experiments which were performed as part of the DiPAR project. The two filled circles represent the targets of the modified Fitts' task, which are touched alternately with the pen-tip.
2.6. References


