Chapter 6

Discussion

In this thesis, we used movement sensors for the quantification of symptoms of movement disorder patients. We defined two goals to drive our research; first, we investigated the use of movement sensors for diagnostic purposes and second, we studied the use of movement sensors for long-term monitoring.

We took two approaches to investigate the applicability of using movement sensors in clinical practice for diagnostic purposes. First, we aimed to improve upon the classification of patients with early onset ataxia (EOA) or developmental coordination disorder (DCD) and healthy participants, by analyzing several movement tests, simultaneously. Second, we investigated the difference in classification performance between knowledge-based and statistical features of movement for the correct identification of these groups.

To investigate the use of movement sensors for long-term monitoring, we focused on tremor monitoring in the home environment. First, we evaluated the relationship between the number of days of recording and the reliability of the quantification of tremor presence, frequency, and intensity. Second, we compared the differences between subjective and objective tremor presence in both functional and organic tremor patients, since patients with functional tremor were previously found to exhibit a large mismatch in objectively determined and self-reported tremor symptoms, in contrast to patients with organic tremor who did not.

In this section, we present a summary of the results, identified challenges, points of improvement and recommendations for future work for each chapter. Finally, we discuss future directions for the use of movement sensors to clinically assess movement disorder patients.

6.1 Main results

Our results suggest that movement sensors could be used as an additional aid for diagnosis (EOA, DCD) and long-term monitoring (tremor) of movement disorder patients. In this section, we summarize the most important findings in this thesis.

To support the diagnosis of ataxia, we first investigated the relevance of adding more tests for the distinction between patients with EOA or DCD and healthy participants. Previous studies in our group found that using only the finger to nose SARA test it was already possible to distinguish these three groups. However, using only the finger to nose test limited accuracy was obtained, especially for the DCD group (Martinez-Manzanera et al., 2018). For this reason, for the studies in this thesis, we recruited more participants and combined information from all three upper limb SARA tests (finger to nose, finger chasing and fast alternating movements). Similar to what experts experience during clinical evaluation, we expected that the combination of two or

more SARA tests would improve the classification of patients with EOA or DCD and healthy participants.

Combining the information extracted from the three SARA tests, indeed allowed improvement of the classification between patients with EAO or DCD and healthy participants. Classification accuracy on group level was 85.6% for EOA patients, 63.5% for DCD patients and 91.2% for healthy participants. In comparison, using only the finger to nose test yielded classification accuracies of 73.7 % for EOA patients, 53.4% for DCD patients and 87.2% for healthy participants (Martinez-Manzanera et al., 2018).

Also, according to the feature importance obtained from the random forest classifier, the combination of these three tests was indeed required to obtain this improvement in classification accuracy. Especially, features from the fast alternating movements and the finger to nose tests were among the top 20 most relevant features. Features from the finger chasing test were found to be less relevant, though, appearing only after place 20 of the most relevant features. This could be explained based on the execution of the test, where especially the youngest children experienced problems while performing the tests, possibly due to the size of the sensor attached to the index finger obstructing voluntary movement.

To further improve the distinction between the EOA and DCD patient groups and healthy participants and building upon our previous knowledge, we also, simultaneously, introduced more movement features based on how clinicians assess symptoms when evaluating SARA test performance. For example, we used the angular velocity of the sensor attached to the wrist to evaluate the smoothness of wrist rotation during the fast alternating movements. For the upper limb SARA tests, we extracted 34 features, of which 25 were based on clinical knowledge and 9 were statistically derived. Similarly, for the lower limb SARA tests, we extracted 32 features, of which 28 were based on clinical knowledge and 4 were statistically derived. For analysis of lower limb tests, we found that the combination of features from different tests also improved the classification and that features based on clinical knowledge were more relevant for the classification of the three groups.

To investigate the use of movement sensors for the long-term monitoring of tremor, we first investigated the number of days needed to reliably quantify tremor, using accelerometer data collected from 36 adult organic tremor (OrgT) and functional tremor (FT) patients. These data were collected during continuous (day-time) monitoring in the home environment for 30 days. There is ample literature regarding the characteristics used to assess tremor. In our study, we included only the tremor characteristics that are most used to assess tremor clinically or in the home environment: tremor presence, frequency, and intensity. Using these characteristics, we aimed for our results to be of relevance for clinicians and movement disorder researchers.

The included patients wore the accelerometers for several days and for several hours every day, which allowed to investigate the minimum number of days and hours per day needed to obtain reliable estimates of tremor characteristics. We found that, although one day with six hours of accelerometry recording is generally sufficient to obtain estimates of tremor presence, tremor frequency variability and tremor intensity with moderate to good reliability, independent of tremor type, three days of tremor recording increases reliability of these tremor characteristics considerably.

Finally, we investigated the relationship between accelerometry based objective tremor duration and diary-based subjective symptom burden in patients with functional tremor (FT) or organic tremor (OrgT). As we did not find differences between patients with FT or OrgT in the subjective or objective evaluation of tremor, our findings have important implications for clinical practice and the design of future studies. First, patients with FT do have tremor for a considerable percentage of time and have no substantial mismatch between objective and subjective symptom burden, contrary to what previous studies seemed to indicate. Therefore, they cannot be regarded as 'merely having a perception problem' or stop trembling as soon as they leave the hospital. Second, this similar association between objective/subjective tremor symptoms and the similar level of psychopathology in patients with FT or OrgT reinforces the need to diagnose FT using positive criteria like entrainment or distraction, thereby omitting the need for "psychogenic" criteria. This is in line with findings in the review of Espay et al., (2018), indicating that 'a diagnosis can now be made in an inclusionary manner by identifying neurological signs that are specific to functional neurological disorders, without reliance on presence or absence of psychological stressors or suggestive historical clues'.

6.2 Recommendations

6.2.1 General

In general, the studies presented in this thesis are only the first steps towards clinical use, since further clinical validation is needed to use them as a clinical support tool. In this section, we present some of the challenges we found regarding the clinical validation of the techniques used for the quantification of symptoms in movement disorder patients and how we approached them. Also, we present some suggestions for future work that could be used to improve upon clinical applicability of movement sensors.

According to Routhier et al., (2020), clinical validations of IMU-based systems are rarely conducted, which could be due to different factors. First, the time required to manage the device(s) and the collected data is an important drawback identified by clinicians when it comes to the use of IMUs. Second, the data typically needs to be processed before being clinically usable and

technical expertise is often needed. Third, it can become cumbersome when data from different IMU systems need to be combined to perform one complete analysis.

Nevertheless, the potential usefulness and influence of IMUs on clinical practice is considered of relevance for the evaluation of movement disorder patients. First, this technology could help to quantitatively profile activities performed outside of the outpatient clinic (e.g., use of limb(s) on the (un)affected side, community/home walking pattern, falls or loss of balance, number of occurrences of a non-recommended movement). Second, such systems could gather quantitative data related to variables that can be more difficult to assess due to their complexity (e.g., gait). This could be useful at follow-up, to discuss progress and compliance with patients. It could also motivate patients and assist self-management (Routhier et al., 2020).

In this thesis, we proposed different approaches to improve upon the use of movement sensors for clinical use, for example with the techniques used to quantify ataxia symptoms or to identify the number of days needed to obtain reliable estimates of tremor characteristics. Nevertheless, we consider that more work is needed in this direction, for example, to reduce the time needed to prepare the movement sensors setup or to develop new techniques to analyse the data. In the following sections, we present some ideas regarding challenges and directions for validation of the use of movement sensors.

6.2.2 Classification of EOA and DCD patients and healthy participants

When studying the use of IMUs to support the diagnosis of ataxia, we identified some issues that can be improved upon to obtain a better performance of the automatic classification of EOA and DCD patients and healthy participants. One of the intentions of our work was to focus on the extraction of meaningful features. For this purpose, we translated clinical knowledge into mathematical expressions, reasoning that using clinical knowledge to characterize the ataxic symptoms could be of additional value during the diagnostic workup.

Unfortunately, there were some clinical characteristics that we were not yet able to translate in this manner, such as the accuracy of voluntary movements during the finger chasing test as expressed in under- or overshoot. We tried to (partially) solve this problem by presenting the targets for the finger-to-nose and finger chase tests on touch screens, so that the distance between the touch of the participants and the presented target could be calculated as an approximation of overshoot. However, patients often touched the screen with a larger part of the hand than just the index fingertip, which hampered the determination of the touch location. Furthermore, the 3D position of the targets on the touch screen and the 3D position of the fingertip derived from the movement sensors could not yet be synchronized, hampering full assessment of under- or overshoot.

Also for gait, where we could reconstruct normal gait and obtain several spatio-temporal features, there are still some relevant clinical features we could not calculate (yet), such as the distance between both feet. This characteristic is relevant to allow assessment of broad-based gait, which is a hallmark of ataxia. One way to solve this problem could be to develop a kinematic model of the lower limbs, adding an extra IMU in the lower back, similar to the model described by Zheng et al., (2014). In this type of model, a kinematic chain is developed to model gait, which probably could be used to obtain this type of feature.

Also, to the best of our knowledge, there is no model to reconstruct tandem gait, and there is scarce literature evaluating this test using movement sensors (Kim et al., 2019; Trojaniello et al., 2015). Since tandem gait assessment is an important aspect of clinical ataxia assessment, it would be useful to create a tandem gait model using inertial data which may then be used to obtain features similar to the normal gait model.

Another technical issue is related to the size of the IMU used for data recording, particularly for assessment of upper limb movements. We used three IMUs to collect data from each arm. Even though the (Shimmer) IMUs are relatively small (51mm x 34mm x 14mm) patients feel uncomfortable using them during fine motor tasks. This is particularly experienced for the IMU that is attached to the index finger, and even more so for the youngest children. This may have reduced the quality of the data we used to extract features, particularly in this latter group. One way to avoid this problem could be to use smart gloves (Henderson et al., 2021; Jalloul, 2018), which have embedded IMUs and which could be adapted for children. With this technology, it could be possible to reduce the constraints during fine motor tasks and improve data quality.

The final point of improvement is the small number of - particularly DCD - patients which yielded imbalanced classes. The number of recruited DCD patients was limited by the nature of our study centre. As a tertiary referral centre, we could only include a limited number of DCD patients. This issue may have caused bias in our results towards the majority group (healthy participants). Even though we implemented a synthetic sampling technique to overcome this issue, a future study could try to include more DCD patients, e.g., by multicenter collaborations.

6.2.3 Tremor quantification

Regarding the assessment of tremor patients in their home environment, we also identified some challenges. We here present the most relevant challenges and opportunities for future work.

We based our tremor identification algorithm on a previous study from our group (Martinez Manzanera et al., 2016), in which we compared different techniques to identify tremor and validated the results from each automatic technique against the assessments from two clinicians (experts). The data used in that study were obtained during clinical assessment of tremor when patients were

executing prescribed upper limb activities. As different types of tremor occur during different postures and movements, an algorithm that can distinguish different activities (Davis et al., 2016), in addition to the algorithm that we used for the detection of tremor, could aid in the differential diagnosis of tremor (e.g., postural, kinetic, intention). Vescio et al., (2021) have recently presented an overview of the literature in the last decade regarding wearable devices for the assessment of tremor, distinguishing between devices for the assessment and characterization of tremor, for monitoring tremor and efficacy of therapies and for differential diagnosis.

With such improvements in techniques for the identification of tremor and types of activities, more personalized assessments of tremor could be derived. Currently, we focused our study on the detection and extraction of full-day measures of tremor, but the pattern of tremor over the day could also be investigated. Patients may present specific tremor (intensity) patterns over the day, e.g., related to their medication intake, or to their activities. A personalized assessment of tremor may therefore help improve the design of treatments. With this goal in mind, algorithms embedded in measurement devices could statistically analyze the sensor-based metrics to identify clinically significant changes in the data over time (Sprint et al., 2016). Existing commercial systems such as BioSensics (BioSensics LLC, USA) offer such IMU-based metrics to evaluate gait, balance and motor symptoms among others. Another example is the personal KineticGraph (Global Kinetics, Australia) which records Parkinson's symptoms and reminds the patient when to take the Parkinson's disease medication as prescribed by the doctor.

Besides the improvements in techniques (algorithms) to quantify symptoms of movement disorder patients, improvements in IMU design might be needed. For example, we investigated a group of patients who wore the devices for several hours (up to 10 hours) every day and during several days (up to 30 days). Improving devices by further reducing their size may help increase usability. Also, reducing the technical setup and use may help to improve usability, for example for kinematic reconstruction of human movement the calibration process may take from 30 up to 60 minutes, although some researchers suggested new techniques to reduce the calibration time to only six minutes (Cheuk et al., 2012).

The general objective of this thesis is to evaluate the use of inertial sensors as an additional aid for diagnosis and monitoring in the study of movement disorder patients. The studies presented here provide a step forward in that direction, even though further clinical validation is needed.

Regarding validation of diagnostic applications, we propose to ask patients to use inertial sensors during daily activities and in the home environment for several days. Such data could then be used to first identify different activities such as walking, standing or sitting, using so-called human activity recognition (HAR) algorithms. Second, once the activities have been identified the algorithms described in this thesis could be implemented to identify which activities and

related features better help to distinguish between EOA, DCD and healthy participants. Finally, the most relevant features from such activities could be used by clinicians and researchers as additional information during the diagnostic workup of EOA and DCD. Furthermore, this information could inspire researchers to develop research and clinical validation studies to create new clinical protocols, similar to the SARA protocol.

Regarding the clinical application of long-term tremor monitoring studies, we think they might help clinicians and researchers to design new assessment protocols or personalized treatment for tremor patients. For example, our results could encourage researchers to investigate the reliability of quantifying other symptoms such as bradykinesia, dyskinesia, postural stability, etc., by using inertial sensors. Additionally, it might be interesting to investigate the potential use of inertial sensors to continuously monitor the effect of different treatments or medication on tremor. In this case, data from an inertial sensor at the most affected limb could be collected and transferred to a mobile phone continuously, without the necessity for the patient to perform specific tasks. Processing could then take place at the phone or at a central server after anonymization and results could be shown in personalized form to the patient, as well as to the treating clinician for online assessment and personalization of treatment. At the same time, the results could be stored for several days to weeks to create a personalized profile of the symptoms. Several such systems are at the market already (Luis-Martínez & et al., 2020), but not many allow for continuous monitoring of tremor without active involvement of the patient. Importantly, our results show that patients can comply with such long-term tremor monitoring (Chapter 5). In this way we hope to have opened up further possibilities for improved home-based personalized healthcare of patients with tremor or other movement disorders.

6.3 Final remark

In this thesis, we studied the use of movement sensors as a support tool in the clinical evaluation of movement disorders, particularly for classification and monitoring, that currently rely on clinical observation. First, we found that combining information from several SARA tests, as well as including movement features based on clinical assessment, improve the classification of EOA and DCD patients and healthy participants. Second, we found that three days of unconstrained tremor recording are sufficient to reliably quantify upper limb tremor. Finally, we showed that subjective and objective assessments of upper limb tremor duration are similar for both OrgT and FT patients. In conclusion, the results obtained in this thesis provide evidence that movement sensors can be used as a support tool for the monitoring and diagnosis of movement disorder patients.

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