

# Wearable sensors for monitoring Epilepsy and Parkinson's disease

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Cover illustration: The upper line indicates acceleration signals during a tonic-clonic seizure; The lower line is an example of evident wearing-off phenomena registered with the Parkinson Kinetigraph (Global Kinetics Corporation, Australia) device where the median bradykinesia score (blue line) worsens prior to each dose reminder time (red lines).

Illustrated by Dongni Johansson Buvarp

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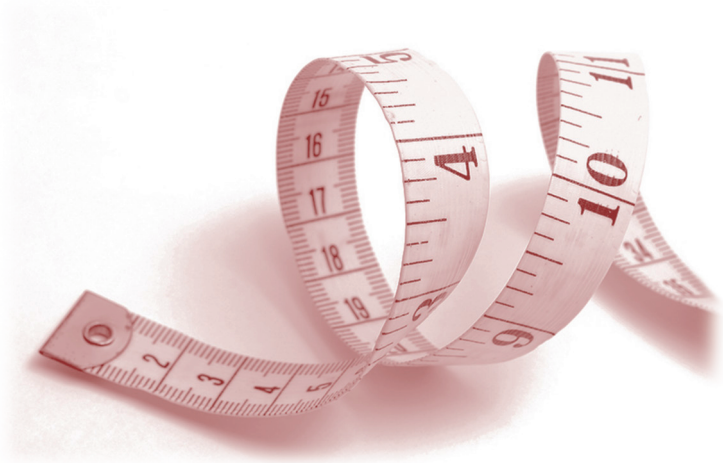
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*To measure is to know*

*Lord Kelvin*





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## Abstract

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**Introduction:** Epilepsy and Parkinson's disease (PD) are conditions where management would benefit greatly from monitoring symptoms over longer time periods in natural everyday environments instead of only intermittent assessments at clinics. Wearable technology with built-in sensors such as accelerometers and gyroscopes, could allow continuous and objective long-term monitoring of movement patterns.

**Aim:** The overall aim of this thesis was to explore and evaluate how wearable sensors can be used in clinical applications with continuously monitored movement related variables in epilepsy and PD.

**Methods:** The studies in the thesis involved both qualitative and quantitative research methods. Perceptions regarding the use of wearable technology in disease monitoring and management as reported by individuals with epilepsy and PD as well as health professionals working with these patient groups were explored using focus group discussions (Paper I). Wrist-worn sensors were used to detect tonic-clonic seizures in epilepsy (Paper II) and to quantify motor levodopa responses in PD (Paper III). The effects of individual dose adjustment based on information derived from wearable sensors were further investigated (Paper IV). The performance of sensor-based algorithms for seizure detection and motor state recognition was evaluated against clinical standard evaluations including video-EEG in epilepsy and clinical assessment scales for PD motor and non-motor symptoms. Adherence and missing data were examined to explore feasibility of using wearables (Paper II-IV).

**Results:** End users saw possible benefits for improved treatment effects with the use of wearable sensors and valued this benefit more than the possible inconvenience of wearing the sensors (Paper I). However, they were concerned about unclear information and inconclusive recordings and some fears about personal integrity were at odds with the expectations on interactivity (Paper I). Wearable sensors showed a high sensitivity and a low false positive rate in detecting tonic-clonic seizures in epilepsy (Paper II). Wearable sensors are useful for automated quantification of PD motor states using instrumental testing as well as passive monitoring (Paper III-IV). The PD motor and non-motor symptoms, disease-specific quality of life and wearing-off symptoms improved after dose titration based on the information provided by a wrist-worn sensor (Paper IV). Adherence to using wearables was high across the studies and missing data was mainly attributed to sensor malfunction.

**Conclusions and clinical implications:** The use of wearable sensors for detecting seizures or quantifying PD motor states showed clinical utility as tools for ascertaining tonic-clonic seizure frequency and monitoring treatment effects in PD outside of hospital. The information provided by sensor monitoring was effective for supporting clinical decision making in PD, indicating that treatment individualization based on wearable sensors is feasible.

### Keywords

Epilepsy, Parkinson's disease, wearable sensors, continuous and objective monitoring, end users' perceptions, qualitative content analysis, machine learning algorithms, tonic-clonic seizure detection, dose titration, motor state recognition

# Sammanfattning på svenska

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Epilepsi och Parkinsons sjukdom är tillstånd där behandlingen skulle gynnas av att kunna följa förekomsten av sjukdomssymptom under längre tidsperioder i naturliga och vardagliga miljöer istället för vid glesa bedömningar på vårdinrättningar. Bärbar teknik med inbyggda sensorer som accelerometrar och gyroskop skulle kunna användas för kontinuerlig långtidsmonitorering av rörelsemönster.

**Syfte:** Det övergripande syftet med denna avhandling var att utforska och utvärdera hur bärbara sensorer kan användas kliniskt för att kontinuerligt mäta rörelserelaterade variabler vid epilepsi och Parkinsons sjukdom.

**Metod:** Studierna som ingår i avhandlingen innefattar både kvalitativa och kvantitativa forskningsmetoder. Fokusgruppintervjuer användes för att undersöka vilka uppfattningar individer med epilepsi eller Parkinsons sjukdom, liksom sjukvårdspersonal, har om att använda bärbar teknologi (delarbete I). Handledsburna sensorer användes för att detektera tonisk-kloniska anfall vid epilepsi (delarbete II), eller för att kvantifiera motoriska symptom vid Parkinsons sjukdom (delarbete III). Dessutom undersöktes effekten av att individuellt justera läkemedelsdoser baserat på information från bärbara sensorer (delarbete IV). Prestandan hos sensorbaserade algoritmer för detektion av anfall och igenkänning av motoriska symptom jämfördes med kliniska standardutvärderingar, inklusive video-EEG vid epilepsi och kliniska utvärderingsskalor för motoriska och icke-motoriska symptom vid Parkinsons sjukdom (delarbete IV). Följsamhet till att bära sensorer och andelen förlorade mätdata undersöktes också för att utforska genomförbarheten med att använda bärbara sensorer (delarbete II-IV).

**Resultat:** Tiltänkta användare såg möjliga fördelar genom förbättrade behandlingseffekter med användning av bärbara sensorer. De värderade denna möjliga fördel högre än det möjliga besväret att bära sensorerna (delarbete I). De uttryckte dock viss oro angående oklar information och att registreringarna inte skulle vara konklusiva, liksom vissa farhågor gällande personlig integritet vilket dock var i konflikt med förväntningarna på interaktivitet (delarbete I). Användningen av rörelsesensorer visade hög sensitivitet och ett lågt falskt positivt värde för detektion av tonisk-kloniska anfall vid epi-

lepsi (delarbete II). Rörelsesensorer är användbara för automatisk kvantifiering av motoriska symptom och medicineringsberoende fluktuationer vid Parkinsons sjukdom under instrumental testning så väl som vid passiv rörelsemätning (delarbete III och IV). De motoriska och icke-motoriska symptomen vid Parkinsons sjukdom, hälso-relaterad livskvalitet samt upplevda symptom på grund av dosglapp förbättrades efter dositering baserad på information från en handledsburen sensor (delarbete IV). Följsamhet till att använda bärbara sensorer var hög i studierna och förlust av mätdata berodde huvudsakligen på bristande funktion i hanteringssystemet.

**Slutsatser och klinisk betydelse:** Bärbara sensorer visade klinisk användbarhet för att detektera tonisk-kloniska anfall vid epilepsi eller kvantifiera motoriska symptom och läkemedelsrelaterade fluktuationer vid Parkinsons sjukdom utanför sjukhusmiljö. Den information man får från rörelsemätning med bärbara sensorer var användbar för att stödja kliniskt beslutsfattande avseende justering av läkemedelsdoser vid Parkinsons sjukdom. Det är möjligt att använda bärbara sensorer för att individualisera behandling.



# List of papers

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*This thesis is based on the following studies, referred to in the text by their Roman numerals.*

- I. Ozanne A\*, Johansson D\*, Hällgren Graneheim U, Malmgren K, Bergquist F, Alt Murphy M. Wearables in epilepsy and Parkinson's disease – A focus group study. *Acta Neurologica Scandinavica* 2018; **137(2)**:188-194.
- II. Johansson D\*, Ohlsson F\*, Krýsl D, Rydenhag B, Czarnecki M, Gustafsson N, Wipenmyr J, McKelvey T, Malmgren K. Tonic-clonic seizure detection using accelerometry-based wearable sensors – a prospective, video-EEG controlled study. *Seizure* 2019; **65**: 48-54
- III. Johansson D\*, Thomas I\*, Ericsson A, Johansson A, Medvedev A, Memedi M, Nyholm D, Ohlsson F, Senek M, Spira J, Westin J, Bergquist F. Evaluation of a sensor algorithm for motor state rating in Parkinson's disease. *Parkinsonism & Related Disorders* 2019; Epub March 26.  
[doi.org/10.1016/j.parkreldis.2019.03.022](https://doi.org/10.1016/j.parkreldis.2019.03.022)
- IV. Johansson D, Ericsson A, Johansson A, Medvedev A, Nyholm D, Ohlsson F, Senek M, Spira J, Thomas I, Westin J, Bergquist F. Individualization of levodopa treatment using a microtablet dispenser and ambulatory accelerometry. *CNS Neuroscience & Therapeutics* 2018; **24(5)**:439-447.

\* Authors contributed equally

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# Abbreviations

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AEDs	Antiepileptic drugs
BKS	Bradykinesia scores
COMT	Catechol-O-methyltransferase
DKS	Dyskinesia scores
ECG	Electrocardiography
EDA	Electrodermal activity
EQ-5D-5L	EuroQoL 5-dimension with five responses
FDS	Fluctuation and dyskinesia score
FP	False positive
HP	Health professional
HRV	Heart rate variability
H&Y	Hoehn and Yahr stage
KNN	K-nearest neighbors
MADRS-S	Montgomery Åsberg Depression Rating Scale
MAO-B	Monoamine oxidase B
MDS-UPDRS	The Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale
NMS	Non-Motor Symptoms in Parkinson's disease
NMS-Quest	Non-Motor Symptoms Questionnaire
PD	Parkinson's disease
PDQ-8	8-item Parkinson's disease questionnaire quality of life
PKG	The Parkinson Kinetigraph data logger
PPG	Photoplethysmography
PTT	Pulse transit time
PwE	Persons with epilepsy
PwPD	Persons with Parkinson's disease
QoL	Quality of life
RF	Random forest
RMSE	Root mean square error
SUDEP	Sudden unexpected death in epilepsy
SVM	Support vector machine
TCS	Tonic-clonic seizure
TP	True positive
TRIS	Treatment Response Index from Sensors
TRS	Treatment Response Scale
UPDRS	Unified Parkinson's Disease Rating Scale
Video-EEG	Video electroencephalography
WOQ-19	19-item Wearing-Off Questionnaire

# Introduction

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Neurological disorders, such as epilepsy and Parkinson's disease (PD), are a major cause of disability and mortality worldwide.<sup>1</sup> Rising life expectancy and population growth globally in past decades lead to an increased prevalence of neurological diseases, which requires large resource allocations to health care.

Wearable technology with built-in sensors can be used to monitor movements and various physiological variables in an objective and continuous fashion. Advances in sensor technology and machine learning algorithms capable of identifying patterns from large, complex and heterogeneous data, have heightened clinical interest in applying these techniques in research and clinical care. The emergence of this new innovative technology might be effective and fulfil the need of both patients and health professionals to achieve better symptom monitoring.

Epilepsy and PD are two neurological conditions where objective signs include motor symptoms as well as changes in other physiological variables. Disease status in individuals with epilepsy or PD is followed by repeated visits at clinics, with long intervals, which can only provide discrete snapshots of symptoms. The monitoring of motor and physiological variables in a natural setting would give a more accurate picture of symptoms and could greatly benefit the disease management in epilepsy and PD.

Wearables are increasingly being applied for detection of epileptic seizures and PD motor symptom monitoring.<sup>2</sup> Clinical evaluation of wearables in the context of neurological disease monitoring is vital to ascertain if these techniques can be used to address clinical needs of both patients and health professionals. This thesis presents four studies where the clinical application of wearable sensors in epilepsy and PD were evaluated in three aspects involving end users' perspectives, feasibility of using wearable sensors from practical experiences and clinical evaluation of algorithm performance to its clinical effectiveness.

# Epilepsy

Epilepsy affects individuals irrespective of age, gender, ethnic background and geographic location.<sup>3</sup> It is the most common chronic neurological disorder with a life-time prevalence of 7.6 per 1,000 persons.<sup>4</sup> There is currently no cure or prevention for epilepsy and 30% of affected persons do not achieve seizure control with pharmacological treatment.<sup>5</sup> In Sweden around 65,000 children and adults have epilepsy and despite adequate drug treatment more than 20,000 of them have uncontrolled seizures.<sup>6</sup>

Epilepsy is characterized by recurrent epileptic seizures caused by uncontrolled, abnormal excessive electrical discharges of brain nerve cells. Seizures are often accompanied with variations in heart rhythm,<sup>7</sup> most often tachycardia but sometimes bradycardia, and may affect oxygen saturation.<sup>8</sup> The hallmark of seizures is their unpredictability, which is stressful as well as potentially dangerous for persons with epilepsy (PwE).

## Classification of the epilepsies

The International League Against Epilepsy (ILAE) has recently presented a comprehensive classification system for the epilepsies which reflects the gain in knowledge and understanding since the last ratified classification from 1989.<sup>9,10</sup> This classification comprises three levels of diagnosis: seizure type, epilepsy type (focal, generalized, combined generalized and focal, unknown) and epilepsy syndrome.<sup>9</sup> At all levels of diagnosis the aim should be to identify the etiology of the patient's epilepsy. A range of etiologic groups have been recognized: structural, genetic, infectious, metabolic, immune and unknown.<sup>4</sup> A patient's epilepsy may be classified into more than one etiologic category.

The classification of *seizure type* is operational, mainly based on clinical seizure manifestations. The basic classification divides seizures into those with *focal onset*, those with *generalized onset* and those with *unknown onset*. Level of awareness is usually included in the seizure type, which in varying detail includes other classifiers e.g. motor and non-motor onset symptoms. A special seizure type which actually reflects a propagation pattern of a seizure is the *focal to bilateral tonic-clonic* (corresponding to partial seizure with secondary generalization in the 1981 classification) which is distinguished from tonic-clonic seizures with

generalized onset. Focal seizures may rapidly engage bilateral networks, whereas classification is based on unilateral onset.

Regardless of whether a tonic-clonic seizure (TCS) has a focal or generalized onset, the further seizure evolution consists of two consecutive motor phases. The first and shortest is the tonic phase with stiffening of all limbs and the second is the clonic phase with rapid rhythmic jerking of limbs and face.

### **Sudden unexpected death in epilepsy - SUDEP**

Mortality is increased in the epilepsy population and the leading cause of death is sudden unexpected death in epilepsy – SUDEP.<sup>11</sup> The risk is especially high in epilepsy patients with a high frequency of TCSs.<sup>12,13</sup> SUDEP is the leading cause of epilepsy-related mortality, representing the second-leading neurological cause of lost patient life-years after stroke (up to 30% of all deaths in an epilepsy population).<sup>14</sup> Increased heart rate variability (HRV), vagal hypertonia and central hypoventilation might be relevant mechanisms for SUDEP and studies in epilepsy monitoring units have found peri-ictal apnoea with oxygen desaturation.<sup>15</sup> Apart from TCS, male gender and nocturnal seizures are among the risk factors for SUDEP.<sup>16</sup> There is increasing evidence that preventing seizures prevents SUDEP. No pharmacological therapy except for antiepileptic drugs reduces SUDEP risk.

### **Treatment of epilepsy**

Pharmacological treatment with antiepileptic drugs (AEDs) is the mainstay of epilepsy treatment. The mechanism of action of AEDs has not yet been fully understood, but in general they act by decreasing neuronal excitation or increasing neuronal inhibition. The choice of drug depends on a number of different aspects including seizure type, epilepsy type, age, gender and possible adverse effects.<sup>17,18</sup> AED treatment is symptomatic: when it is successful seizures may be abolished but AEDs do not cure the epilepsy. An individual treatment strategy with careful clinical monitoring might minimize the adverse effects of AEDs while optimizing seizure management. For many PwE the seizures are easy to treat with low doses of one appropriately chosen drug (monotherapy). For the approximately 30% of PwE who do not become seizure-free but have a drug resistant epilepsy,<sup>5</sup> many different AEDs may be tested in increasing doses as well as in combination (polytherapy). AED side effects increase with the increasing drug burden and adverse effects of medication have been shown

to be a far more important determinant of health-related quality of life in patients with drug resistant epilepsy than seizures themselves.<sup>19-23</sup>

There are also a number of non-pharmacological treatment options for epilepsy. Among several surgical possibilities the most common is resective epilepsy surgery where the seizure onset zone is identified through advanced neuroimaging and seizure monitoring methods. Other treatments include neuromodulation and the ketogenic diet.

### **Diagnosis and follow-up**

The diagnosis of epilepsy is mainly based on a carefully taken history from the patients and whenever possible also from a witness. The diagnosis therefore to a large extent relies on the clinical experience of the physician as well as on the quality of the information provided by the patients and the witnesses. Several studies have focused on the shortcomings of such clinical diagnoses.<sup>24-31</sup>

In patients with drug resistant epilepsy or in patients where the epilepsy diagnosis is questioned, simultaneous video and electroencephalography (video-EEG) are potent diagnostic tools. The availability is limited though, and the resource is mainly used for presurgical seizure monitoring. This difficulty to ascertain patients' seizure situation is therefore a major issue not only complicating the optimization of treatment in general, but it may risk patients' lives, since it is not possible to optimize treatment for patients at risk for SUDEP if nocturnal TCSs pass unnoticed. This is a strong motivator for implementing new medical devices which could make it possible to monitor seizures objectively. Several such systems are presently being developed.<sup>32-34</sup>



## Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder that affects approximately 20,000 individuals in Sweden.<sup>35</sup> It is a common neurodegenerative disorder second in incidence only to Alzheimer's disease. The number of individuals with PD is projected to increase by more than 50% worldwide by 2030.<sup>36</sup> The risk of developing idiopathic PD is usually multifactorial. Male gender and older age are among the risk factors.<sup>37-39</sup>

PD is characterized by symptoms related to the loss of dopaminergic neurons in the substantia nigra pars compacta. The dopamine deficiency within the basal ganglia leads to an inability to maintain the speed and amplitude of self-paced alternating movements, which results in the mandatory motor sign, bradykinesia. As PD progresses, disability often worsens and can have a very significant negative impact on daily activities, quality of life and in a longer perspective, result in an increased need of assistance from caregivers.

### Motor and non-motor symptoms

When the cardinal motor symptom bradykinesia is observed together with rigidity and/or resting tremor (and sometimes postural instability) the syndrome diagnosis Parkinsonism can be made. The initial manifestation of bradykinesia often includes difficulties in performing activities of daily living that require fine motor control (e.g. using cutlery or doing up buttons on clothes). Resting tremor occurs in some patients and can be observed when the affected body part is in a rest position and disappears with action and during sleep. Rigidity refers to expressed as an increased muscular resistance to a passive movement of a joint.

Non-motor symptoms (NMSs) include autonomic dysfunction, sleep behavior disorders, sensory abnormalities and neuropsychiatric disturbances. NMSs occur throughout the disease from early on to a later stage of PD and can manifest many years prior to the presence of motor symptoms.<sup>40</sup> NMSs might be connected to non-dopaminergic-cell dysfunction as a reflection of deficits in various functions of the central nerve system and the autonomic nervous system. The development of NMSs can be the dominant clinical presentation at the later stage of PD.<sup>41,42</sup> NMSs are usually less well recognized and often undeclared by persons with PD

(PwPD),<sup>43</sup> and cause more burden than motor symptoms as a major determinant of health-related quality of life.<sup>44</sup>

### **Symptoms fluctuation**

The current pharmacological treatments are symptomatic and include dopaminergic drugs like levodopa and dopamine agonists, as well as some drugs which act on other receptor systems (like anticholinergic agents and amantadine). Levodopa remains the most effective symptomatic treatment of PD. After an initial honeymoon period, the response to treatment changes and the therapeutic window becomes narrower as a result of decreased storage capacity of the dopaminergic neurons.<sup>45-47</sup> The duration of efficacy of levodopa shortens from initially 5 hours to 1-3 hours.<sup>48</sup>

After 3-5 years of treatment, up to 80% of patients have motor fluctuations.<sup>49,50</sup> Motor fluctuations can include excessive voluntary movements, dyskinesia and may co-exist with non-motor fluctuations. Motor fluctuations and dyskinesia can be very disabling and increase the need for a more individualized treatment regime to achieve a balance between pharmacological benefits and motor complications.<sup>48,51</sup>

### **Management of motor complications**

To reduce the frequency of “off” time without inducing dyskinesia,<sup>52,53</sup> levodopa dosing schedules are gradually adjusted. Dose fractionation is a strategy where the daily oral dose of levodopa is divided into many smaller doses to stabilize the brain dopamine concentrations as much as possible. However, the published evidence for the efficacy of this strategy is scarce. The clinical argument is mainly based upon pharmacokinetic knowledge and clinical experience of dose fractionation. An increase in dose frequency can have the negative effect of reduced medication compliance and the need for fractioning must therefore be balanced against the trouble of adhering to a complicated schedule. The options for fine-tuning levodopa dosage with traditional oral tablets was previously limited to dose adjustments of 25 mg levodopa per dose, but recently a microtablet formulation of levodopa-carbidopa 5/1.25 mg (Flexilev®, Sensidose AB, Sollentuna, Sweden), was introduced.<sup>54</sup>

### **Clinical assessments of PD symptoms**

In everyday practice much of the clinical assessment is performed as informal interviews and limited clinical examination. Clinical rating scales

can be used for assisting physicians in assessing PD-related disability and impairment. As PD symptoms and disease progression encompass large intra- and inter individual variations, a number of rating scales have been developed in the attempts to better recognize under reported elements of PD impairment and disability. Most clinical instruments require trained raters and can be too time consuming to perform in a standard clinical visit. The clinical instruments are therefore mainly used to address research needs of a standardized process in clinical trials to assess relevant outcomes.

The best established rating scales for assessing global PD symptoms are the Unified Parkinson's Disease Rating Scale (UPDRS) and The Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), which both require 20 to 30 minutes to conduct. The most frequently used scale for assessing non-motor symptoms are the Non-Motor Symptoms Scale and the self-assessed questionnaire Non-motor symptoms Questionnaire (NMS-Quest).<sup>55</sup> Individually experienced NMS symptoms can be diverse among PwPD. Several instruments were also developed to assess particular NMS.<sup>41,56</sup>

The evaluation of symptom fluctuation is based on a retrospective and comprehensive history taken by the physician. PwPD can be asked to keep a detailed diary to carefully record symptoms and treatment effects in relation to dose and duration, such as to recording complete "off", partial "off", complete "on" and "on" with dyskinesia states. To achieve stable assessments and reliable therapeutic decisions, patients might have to keep records every 30 minutes for up to 10 days.<sup>57</sup> The widely used instrument is the 19-item Wearing Off Questionnaire (WOQ-19)<sup>58</sup> which is a self-assessed questionnaire for assessing the occurrence of medication intake related to variations in motor and non-motor symptoms.

## Shared issues of disease management in epilepsy and PD

Epilepsy and PD are two neurological diseases that share some similar challenges in disease management. Objective and quantitative monitoring of epilepsy and PD over time in the patients' natural environments can provide more detailed and specific data on seizure frequency as well as PD symptoms. There are two shared issues of disease management in epilepsy and PD: limitations of self-report and limitations of clinical assessments.

### Limitations of self-report

Monitoring of seizure frequency in epilepsy or PD symptoms is mostly done through self-reporting. Self-reported diaries are subjective and retrospective in nature and are prone to recall-and emotional bias.

In epilepsy, although most PwE are highly motivated to track their seizures, several studies have shown that self-reporting of seizure frequency and severity is highly unreliable, especially for temporal lobe seizures and nocturnal seizures.<sup>26,28,31,59,60</sup> One study showed that 62% of day time seizure accounts were well-documented but only 35% of nocturnal seizures were recorded.<sup>61</sup> Most neurologists underline self-reporting as important when they determine the best course of AED treatments while they are also well aware of a considerable disagreement between the actual seizure frequency and the self-reported data.<sup>33</sup>

In PD, limitation of self-report is related to low adherence to diaries and diary fatigue that occurs in PwPD.<sup>62,63</sup> Also, patients might have difficulty recognizing different functional states (e.g. problems differing between dyskinesia and tremor), and difficulty understanding terminologies that are used by clinicians may hinder patients to correctly describing symptoms. Eventually, this can result in difficulties interpreting the diaries and insufficient information for making treatment decisions. To keep a detailed diary for documenting a variety of symptoms in relation to medication intake times makes the method untenable for many patients.

### Limitations of clinical assessments

In epilepsy, the accessibility of the gold standard, video-EEG, is mainly limited to hospitals. Video-EEG is a diagnostic procedure which often

requires AED reduction and provides little information about the seizure frequency in patient's daily life. Seizure detection based on scalp-EEG signals are sensitive to artifacts<sup>64</sup> and most patients expressed that they would not wear scalp EEG electrodes on a long-term basis.<sup>65</sup>

In PD, most clinical scales contain a few ordinal levels to score individual PD symptoms and they assess a rather abstract "average of symptoms experienced during the past week", rather than day-to-day or hour-to-hour variations. The validated rating scales that are available for clinical assessments focus on efficacy whereas effect duration is usually evaluated based on patient recall at intermittent hospital visits. Assessors are easily influenced by global symptoms to score a clinical rating because of the limitation of human eyes. The minute changes in fine motor performance, such as finger tapping, are difficult to assess through clinical observations.

# Wearables

*Wearables* is the common term for devices integrated in garments or designed as wearable accessories. Wearables with built-in sensors such as accelerometers, gyroscopes and optical sensors allow continuous long-term monitoring of movement and physiological variables.

## Inertial sensors

Inertial measurement units commonly consist of a 3-axial accelerometer and a 3-axial gyroscope, which measure linear acceleration and angular velocity vector components along three orthogonal axes, respectively. Inertial sensors are useful for measuring body movements and tracking body positions in different environments. Inertial sensors are increasingly being applied to quantify gait related activities,<sup>66</sup> posture, physical activity,<sup>67</sup> fall risk,<sup>68,69</sup> arm movements and energy expenditure.<sup>70</sup>

## Machine learning algorithms

Machine learning algorithms are methods that allow autonomous analysis to uncover patterns in large quantities of data. The development of machine learning algorithms can be supervised or unsupervised. Unsupervised machine learning does not rely on a classified data set but uses the input data to identify patterns, clusters, inherent to the input data set. Examples include *hierarchical clustering* and *k-mean*. Supervised machine learning algorithms, like linear and logistic regression, support vector machine (SVM), K-nearest neighbors (KNN) or random forest (RF), uses a classified data set where the outcome is mapped on a known target. Examples of where supervised machine learning has been used include image classification e.g. if it is an apple or a pear, and targeted commercials on Facebook or Youtube based on age, gender and web history.

## Wearables for monitoring epilepsy and PD

Tonic-clonic seizure (TCS) detection is clinically urgent as a high frequency of TCSs has been shown to be associated with sudden unexpected death in epilepsy (SUDEP).<sup>12,13</sup> Accelerometry-based sensors, worn on wrists or upper arms, can detect seizures involving motor phenomena<sup>71-75</sup> including TCSs. The sensitivity of TCS detection varies depending on if one modality or more modalities (e.g. accelerometry,<sup>75-79</sup> electromyography<sup>80-83</sup> or heart rate<sup>84</sup>) are used and the false positive rates are an

issue.<sup>81,85-87</sup> Standardized evaluation of wearables for detecting TCSs is desirable to ensure the performance of detection algorithms.<sup>88,89</sup>

In PD, sensors have mainly been used to measure motor symptoms and motor complications.<sup>2</sup> Bradykinesia, tremor and dyskinesia are measurable symptoms that reflect changes in dopamine transmission.<sup>90</sup> The objective measurements of these symptoms would provide more granular information than traditional assessments about dose adjustment in PD. It remains to be determined if the use of wearables for monitoring PD motor symptoms will improve clinically relevant outcomes.<sup>91</sup>

End users' acceptance and preferences are critical perspectives of usability and feasibility.<sup>92</sup> A qualitative synthesis based on interviews and focus groups studies showed that individuals with neurological disease are in general positive toward using wearables in their daily environment.<sup>2</sup> The potential stigmatization from wearing a "disease indicator" has to be considered in the design of wearable devices.<sup>2</sup> The knowledge of the main facilitators and barriers regarding wearables from end users' perspectives explored in qualitative research (e.g. interviews or focus group discussions) may facilitate implementation of wearables in clinical reality.<sup>93,94</sup>

Adherence to using wearables can be heavily influenced by poor design, e.g. a design that makes it difficult to start and stop measurements or necessitates frequent battery recharge. Missing data attributable to technical errors and/or human factors has been reported to be in the range of 4 to 22% when monitoring neurological diseases.<sup>2</sup> Technical failures such as synchronization failure and data storage problems are common reasons for missing data. However, in the majority of studies of wearables the amount of missing data is not well reported.<sup>2</sup>

There is consequently a need to evaluate whether wearable sensors can meet the needs of both the patients and the health professionals and if they can effectively measure disease indicators in a way that leads to clinically relevant improvements in outcomes. Both qualitative and quantitative knowledge are vital to explore the possible clinical applications of wearables for monitoring epilepsy and PD.

# Aims

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The overall aim of this thesis was to explore and evaluate how wearable sensors can be used in clinical applications for continuous monitoring of epilepsy and PD.

The aims of the individual studies were to:

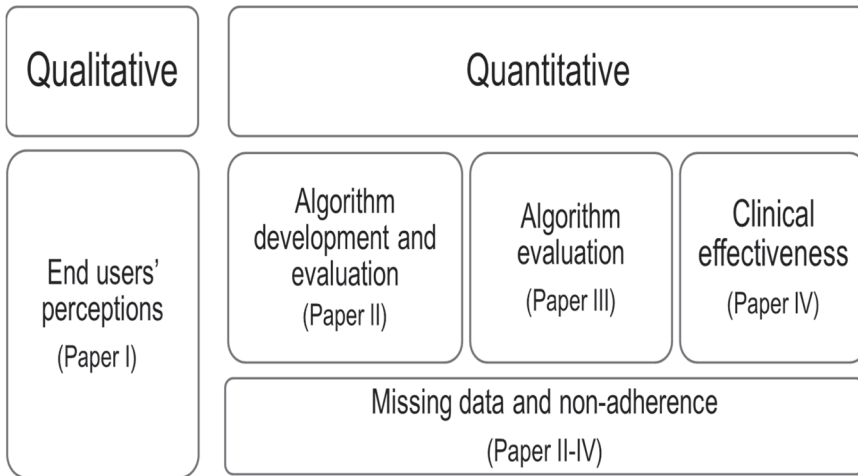
- I. Explore perceptions regarding the use of wearable technology in disease monitoring and management as reported by individuals with epilepsy and PD as well as health professionals working with these patient groups (Paper I).
- II. Evaluate the performance of classification algorithms to detect tonic-clonic seizures using accelerometry data (Paper II).
- III. Evaluate the performance of a previously developed accelerometry-based algorithm for recognizing PD motor states (Paper III).
- IV. Evaluate the effect of using objective free-living motor symptom monitoring to support dose adjustments with a levodopa microtablet dose dispenser in PwPD (Paper IV).



# Methods

## Study design and population

The studies involved both qualitative and quantitative methods. Qualitative analysis was used to explore perceptions regarding the use of wearables from end users' perspectives, and quantitative studies were conducted to evaluate the performance of wearable devices for detecting TCSs in epilepsy and monitoring motor states in PD. Overview of the studies is presented in Figure 1 and study populations, designs, recruitment and data analyses are presented in Table 1.



**Figure 1.** Overview of Paper I-IV

## Ethics

All study participants were recruited from the Sahlgrenska University Hospital, Gothenburg, Sweden. Study protocols were approved by The Regional ethical review board in Gothenburg, Sweden. The studies were conducted in accordance with the Declaration of Helsinki and written informed consent was obtained from all participants.

**Table 1.** Overview of study population, design, recruitment and data analysis.

	Paper I	Paper II	Paper III	Paper IV
<b>Study population</b>	PwE = 10 PwPD = 15 HP-E = 7 HP-PD = 8	PwE = 75	PwPD = 25 <sup>a</sup>	PwPD = 28 <sup>a,b</sup>
<b>Study design</b>	Qualitative exploratory	Prospective	Cross-sectional	Longitudinal observational and open-label
<b>Recruitment</b>	Convenient purposeful sample	Consecutive inclusion	Convenient sample	Convenient sample
<b>Data analysis</b>	Exploration of end users' perceptions	Analysis of accuracy	Analysis of relationship	Analysis of outcomes change over time

<sup>a</sup> Paper III and IV both involved the same study population of 25 participants.

<sup>b</sup> Twenty-eight participants conducted assessments at baseline and 24 participants completed the study.

PwE, persons with epilepsy; PwPD, persons with Parkinson's disease; HP-E, health professionals working with epilepsy; HP-PD, health professionals working with Parkinson' disease.

## Data and statistical analysis

Qualitative content analysis was conducted in Paper I. Statistical analyses in Paper II-IV were performed using IBM SPSS Statistics 22 (IBM Corp., Armonk, NY) or SAS 9.2 (SAS Institute, Cary, NC). Significance was defined as  $P < 0.05$ . Bonferroni adjustment for multiple comparisons was used in Paper IV. Signal processing of sensor data and algorithm development in Paper II-IV were conducted in MATLAB 2016b (MathWorks, USA) or R 3.3.0 (R Foundation for Statistical Computing, Austria). Details of data and statistical analyses are provided in Table 2.

**Table 2.** Details of data and statistical analyses in Paper I-IV.

	Paper I	Paper II	Paper III	Paper IV
<b>Analysis</b>				
<b>Qualitative content analysis</b>	√			
<b>Statistical analysis</b>		√	√	√
<b>Descriptive statistics</b>	√	√	√	√
<b>Analysis of accuracy</b>				
Sensitivity and false positive		√		
<b>Analysis of relationships</b>				
Spearman rank-order correlation			√	
<b>Analysis of changes over time</b>				
Paired t-test			√	√
Wilcoxon's signed ranks test			√	√
Repeated measures analysis of variance				√
Friedman test				√
Effect size (Partial Eta squared, $\eta$ )				√

## Qualitative study (Paper I)

### Focus group discussions

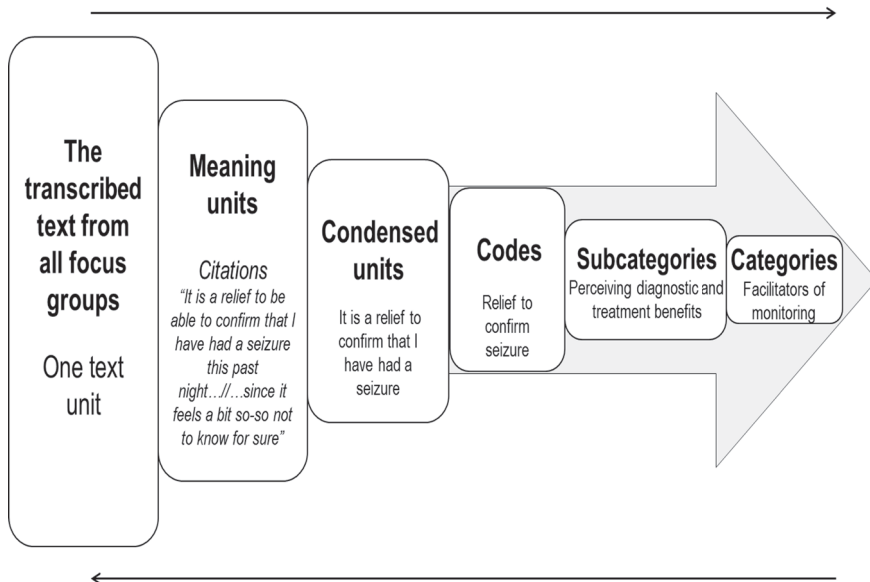
Focus group methodology shares basic assumptions with social constructivism in the sense that the individual's knowledge is constructed and developed through the interaction with others.<sup>95</sup> A focus group is conducted with people from the target group based on commonality and shared experiences to discuss a defined area of interest. The aim is to observe group interactions in order to generate rich narrative descriptions, by increasing awareness of different aspects to the topic.<sup>96</sup> Each group discussion is usually conducted with 5 to 10 people and led by an experienced moderator who ensures that the discussion is focused on the topic. An assistant moderator can also be needed to observe and note participants' body language and expressions to achieve a higher interpretation level.<sup>97</sup>

In Paper I there were eight focus groups with 40 participants, including PwE, PwPD, and health professionals (HPs). The participants were asked to describe their perceptions regarding the use of wearable technology including sensors as well as a garment with multiple integrated sensors. Both the sensors and the garment were presented during the focus group discussions. A purposeful sampling was achieved based on homogeneity

and heterogeneity in each group discussion.<sup>97,98</sup> Homogeneity in each patient focus group was based on gender and diagnosis to allow participants to discuss freely regarding their perceptions, and in each health professional group homogeneity was based on working with either epilepsy or PD. Heterogeneity in each focus group was based on age, previous experience of wearables and in patients also functioning levels. Details of demographics and other characteristics of participants are provided in Paper I, Table 1.

### Qualitative content analysis

A qualitative content analysis with an inductive approach was used to analyze data with the purpose to descriptively examine variations in perceptions regarding the use of wearable technology.<sup>99</sup> Qualitative content analysis focuses on subject and context, and emphasizes differences between and similarities within parts of the text while it deals with manifest and latent content in the text.<sup>99</sup> Manifest content refers to the visible and obvious content that can be categorized with little interpretation while latent content is more interpretative of the underlying meaning of the text.<sup>99</sup>



**Figure 2.** Illustration of a qualitative content analysis process. Examples of citations, condensed units, codes, subcategories and categories are shown. More examples of dialogue citations from focus group discussions are presented in Paper I, Table 2.

The text from all focus groups in Paper I was regarded as a text unit. The text was divided into meaning units, focusing on the manifest content close to the text. The meaning units were condensed into codes which were sorted and abstracted into subcategories based on similarities and differences. The subcategories were then abstracted to categories. The analytic process contained a back and forth movement between the original text and its parts. An example of analytic process is illustrated in Figure 2.

## **Quantitative studies (Paper II-IV)**

### **Participants**

Paper II was conducted with adult epilepsy surgery candidates who underwent scalp or invasive video-EEG recordings at the Epilepsy Monitoring Unit at Sahlgrenska University Hospital. No preselection of patients was applied in this prospective study and there was no specific protocol regarding antiepileptic drug reduction during video-EEG monitoring. The demographic data is presented in Paper II Table 1.

Paper III and IV were conducted with patients who had a diagnosis of idiopathic PD according to the UK Parkinson Disease Society Brain Bank Criteria, and were older than 18 years. Medical prescription records of participants were reviewed to assess eligibility. Participants were eligible for the study if they had stable levodopa medications at intervals of up to 4 hours for at least four weeks before the start of the study. All concomitant PD treatments including catechol-O-methyl transferase inhibitors, monoamine oxidase B inhibitors, and dopamine agonists were allowed. Details of inclusion and exclusion criteria are presented in Paper IV Supplementary Figure 1.

## **Procedures and data acquisition**

### **Wearable devices**

Signals from sensors worn uni- or bilaterally were used in Paper II-IV. Shimmer sensors (Shimmer3, Shimmer Research, Ireland) were used for both Paper II (later phase) and III to collect data from individuals with epilepsy and PD. Shimmer3 are inertial sensors consisting of a tri-axial accelerometer and a tri-axial gyroscope. Another accelerometer (in-house developed sensor, RISE Acreo, Sweden) was used in the early phase of Paper II data collection. An ambulatory monitoring and accelerometry-based device, the Parkinson KinetiGraph (PKG, Global Kinetics Corpo-

ration, Australia), was used in Paper IV. Details of sampling frequency and measurement range are presented in Table 3.

In Paper II the participants wore one accelerometry sensor on each wrist. In Paper III the participants wore one sensor on the dorsum of each wrist and the lateral aspect of each ankle, but only the wrist sensor signals were used for data analysis. In Paper IV the participants wore the PKG at the most affected wrist (Figure 3).

The PKG is a small, portable, wrist-worn watch-like device for quantifying tremor, bradykinesia, dyskinesia and immobility in a free-living environment over a 6-day period.<sup>100</sup> The PKG has recently been approved by the US Food and Drug Administration and has a CE marking. The PKG data is analyzed with proprietary algorithms that generate a bradykinesia score (BKS) and a dyskinesia score (DKS) in 2-minute bins.<sup>100,101</sup> An objective fluctuation and dyskinesia score (FDS) is further derived from the interquartile range of BKS and DKS.<sup>101</sup>

**Table 3.** Overview of measurement range, sampling rate, sensor location and algorithm used in Paper II-IV

	Paper II	Paper III	Paper IV
<b>Signal</b>	Accelerometry	Accelerometry and gyroscope	Accelerometry
<b>Measurement range</b>	±3g Acreo ±8g Shimmer3	Accelerometer ±16g Gyroscope ±2000 dps	±4g
<b>Sampling frequency</b>	50 Hz Acreo 102.4 Hz Shimmer3	102.4 Hz	50 Hz
<b>Sensor location</b>	Bilateral wrists	Bilateral wrists	Wrist-worn on the most affected side
<b>Algorithm</b>	Classification algorithms	Classification algorithms	Commercial proprietary algorithms
<b>Algorithm development and evaluation</b>	Training sets: several algorithms Test sets: KNN, SVM and RF	Initial population: several algorithms New population: SVM	Fuzzy logic
<b>Parameters</b>	Time-frequency domain features	Eighty-eight spatio-temporal features	Lower acceleration and amplitude and with longer intervals between movements



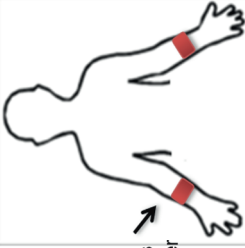


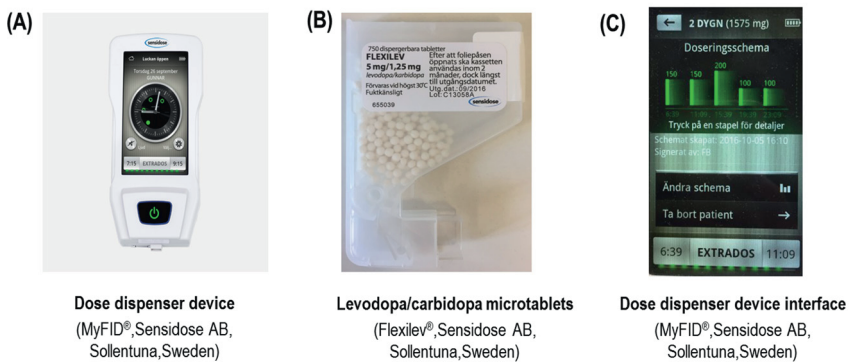
					
<b>Population</b>	Paper II PwE	Shimmer sensors (Shimmer3, Shimmer Research, Ireland)	Paper III PwPD	Paper IV PwPD	PKG (Global Kinetics Corporation, Australia)* *Worn on the most affect wrist
<b>Clinical purpose</b>	TCS detection		Motor state rating	Dose titration	
<b>Wearables</b>	Acreo Shimmer Sensors		Shimmer Sensors		PKG
<b>Variable</b>	Movement related		Movement related	Movement related	
<b>Task</b>	Free-activity		Repeated instrumental tasks	Free movement	
<b>Setting</b>	Hospital		Laboratory	Free-living	
<b>Reference standard</b>	Video-EEG		Clinical ratings	Clinical ratings	Self-assessed questionnaires

Figure 3. A summary of clinical purposes, wearable devices, applied settings and reference standards for Paper II-IV.

In addition to the objective monitoring device (PKG) used in Paper IV, a microtablets dose dispenser device (MyFID<sup>®</sup>, Sensidose AB, Sollentuna, Sweden) was used for fine tuning levodopa dose (Figure 4a and 4b). A microtablet formulation of levodopa-carbidopa (Flexilev<sup>®</sup>, Sensidose AB, Sollentuna, Sweden) has recently been approved by medical products agencies in 14 European countries. The 5/1.25 mg levodopa-carbidopa microtablets offer possibilities to fine-tune and individualize dosage,<sup>102</sup> which can lead to a more stable levodopa plasma concentration.<sup>54</sup> The MyFID device also reminds the patient to take doses and keeps track of adherence. An example of a programmed dosing schedule is presented in Figure 4c.



**Figure 4.** Microtablets dosing system. (a) Dose dispenser device. (b) Levodopa-carbidopa microtablets, 5/1.25 mg. (c) An example of programmed dose schedules.

## Tonic-clonic detection in epilepsy (Paper II)

In this prospective, video-EEG controlled study, patients were confined to the ward room but could move freely between the bed and an arm-chair. In this setting, there were no specific movement restrictions. Seizure timing, duration and types of TCSs (e.g. focal, generalized or unknown) recorded during video-EEG were reviewed and annotated by an experienced epileptologist. The epileptologist was blinded to the sensor data during video-EEG inspection and seizure labelling. The estimated seizure onset and duration for each TCS, according to the annotation, was manually labelled on the accelerometer data. If there were any uncertainties regarding seizure semiology, onset or duration, additional consultation and review of the video-EEG was conducted.

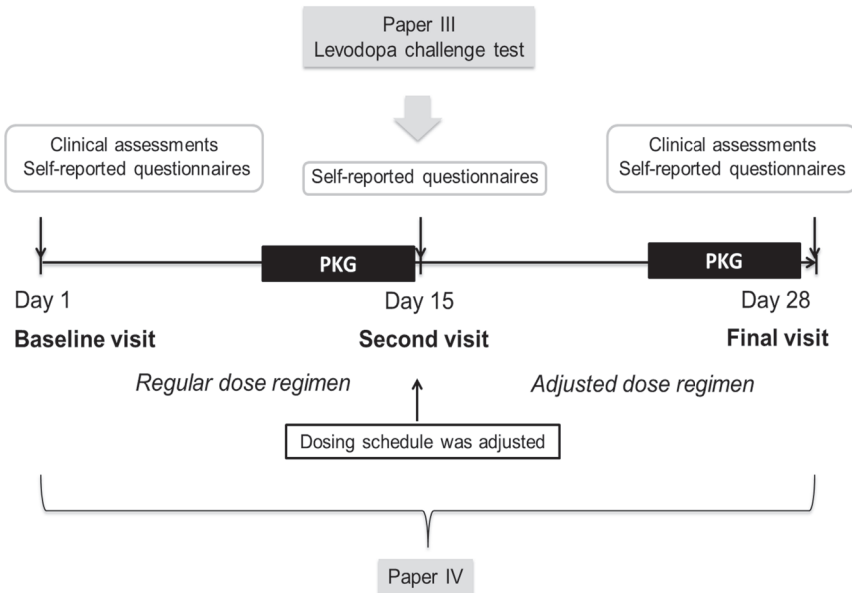


## Motor state rating and individualized treatments in PD (Paper III and IV)

Paper III and IV both involved the same study population of 25 participants. The designs for data collection of Paper III and IV are presented in Figure 5.

### Instrumental testing

Paper III has a cross-sectional design and was conducted during a levodopa challenge test. The purpose was to use inertial sensors to detect changes in instrumental test performance reflecting the individual response to levodopa intake from a practically defined *off* state (off levodopa for at least 12 hours) to best mobility and/or evoked dyskinesia and back to the *off* state. The instrumental tests included hand pronation-supination movements, finger and foot tapping, standing up from sitting, walking across the room and reading a text. These motor tasks were repeated at predetermined time points and all tasks were video recorded for later clinical rating.



**Figure 5.** The data collection process for Paper III and IV.

An accelerometry derived treatment-response index (TRIS) was previously developed in an initial PD sample population. TRIS uses signals from wrist-worn sensors during a pronation-supination movement to score each patient's motor status in term of bradykinesia and dyskinesia at the time of the pronation-supination test.<sup>103,104</sup> TRIS is a continuous index ranging from -3 (severe Parkinsonism) to +3 (dyskinesia), and was developed and mapped on the clinical Treatment Response Scale (TRS).<sup>104</sup> The measurement properties of TRIS with regard to levodopa plasma levels and pharmacodynamic effects were examined in a previous study.<sup>103</sup> In the original population TRIS had a good correlation to clinical assessments of motor state, both TRS and selected items of the unified Parkinson's disease rating scale (UPDRS) part III.<sup>104</sup>

In Paper III TRIS was evaluated against clinical ratings in a new independent PD population. Clinical ratings included TRS and items selected from the UPDRS part III: finger tapping (item 23), rapid alternating movement of hands (item 25), leg agility (item 26), arising from chair (item 27), gait (item 29) as well as body bradykinesia and hypokinesia (item 31). Each item was scored on a 5-level ordinal scale (0=normal and 4=can barely perform the task).<sup>105,106</sup> The maximum level of UPDRS scores of the selected items is 24 points and corresponds to severe Parkinsonism. Dyskinesia was assessed using the definitions of the Dyskinesia Rating Scale also with a 5-point ordinal scale (0=absent, 4= violent dyskinesias, incompatible with any normal motor tasks).<sup>107</sup> The clinical global response to medication was assessed using the TRS. The TRS interval -1 to +1 was defined as functional "on", the interval -3 to -2 indicates severe to moderate Parkinsonism and the interval +2 to +3 indicates "on" with moderate to severe dyskinesia.<sup>108</sup> *Best on* was defined as the maximum TRS value that occurred between  $> -3$  and  $\leq +1$  during the test, and was used to evaluate the maximum motor improvement after the administered levodopa dose.

#### **Passive monitoring and dose titration (Paper IV)**

Paper IV is a four-week open label observational study. Participants used the levodopa-carbidopa microtablets dose dispenser to replace their regular dosing schedule after translating their levodopa preparation to levodopa-carbidopa microtablets, 5/1.25 mg. The medication schedules were adjusted after the first two weeks of using the microtablets dose dispenser with the patient's regular dosing schedule (Figure 5). The individual dose adjustment was based on objective information that was generated from a

week long objective measurement (PKG) after confirming the content in a short clinical interview. Different outcome measures in terms of PD motor and non-motor symptoms and quality of life were assessed at baseline, as well as before the medication adjustment, and two weeks after medication adjustment.

Clinical assessments and self-reported questionnaires were used to assess the clinical effects of adjusting microtablet dose schedules based on passive accelerometry monitoring. The global PD symptoms were assessed using MDS-UPDRS. The MDS-UPDRS includes four parts with in total 65 items: Part I (Non-motor Experiences of Daily Living), Part II (Motor Experiences of Daily Living), Part III (Motor Examination) and Part IV (Motor Complications).<sup>109</sup> Each item consists of 5 ordinal responses (0=normal to 4=severe).

Non-motor PD symptoms were assessed using the non-motor symptoms self-assessed questionnaire.<sup>41</sup> Health related quality of life was assessed with the 8-item patient rated Parkinson's disease questionnaire (PDQ-8) quality-of-life.<sup>110</sup> For the same purpose, EuroQoL 5-dimension with five responses (EQ-5D-5L) was also used.<sup>111</sup> Furthermore, Montgomery Åsberg Depression Rating Scale self-reported questionnaire (MADRS-S) is a 9-item scale ranging from 0 to 6 (higher is more severe) for measuring depressive symptoms.<sup>112,113</sup>

## **Algorithm development and evaluations**

### **Tonic-clonic seizure detection (Paper II)**

Algorithm detection performance was evaluated in term of sensitivity and false positive rates. High frequency and/or large amplitude movements during normal activities, which may be mistaken for seizure activity in sensor data (e.g. brushing teeth and washing dishes), were also included in the algorithm training data set to evaluate the detection performance against false positives. During the model development phase,<sup>114</sup> the training set data was used to evaluate several classification algorithms including linear regressions, K-nearest neighbors (KNN), support vector machine (SVM), quadratic discriminant analysis and random forest (RF) to optimize the feature set. The binary outcome, i.e. seizure (1) and non-seizure (0), is provided by the classification algorithms. A strict separation of the training data sets for the development phase and the testing data sets for the evaluation phase was carried out to avoid overestimation of the algorithm performance.

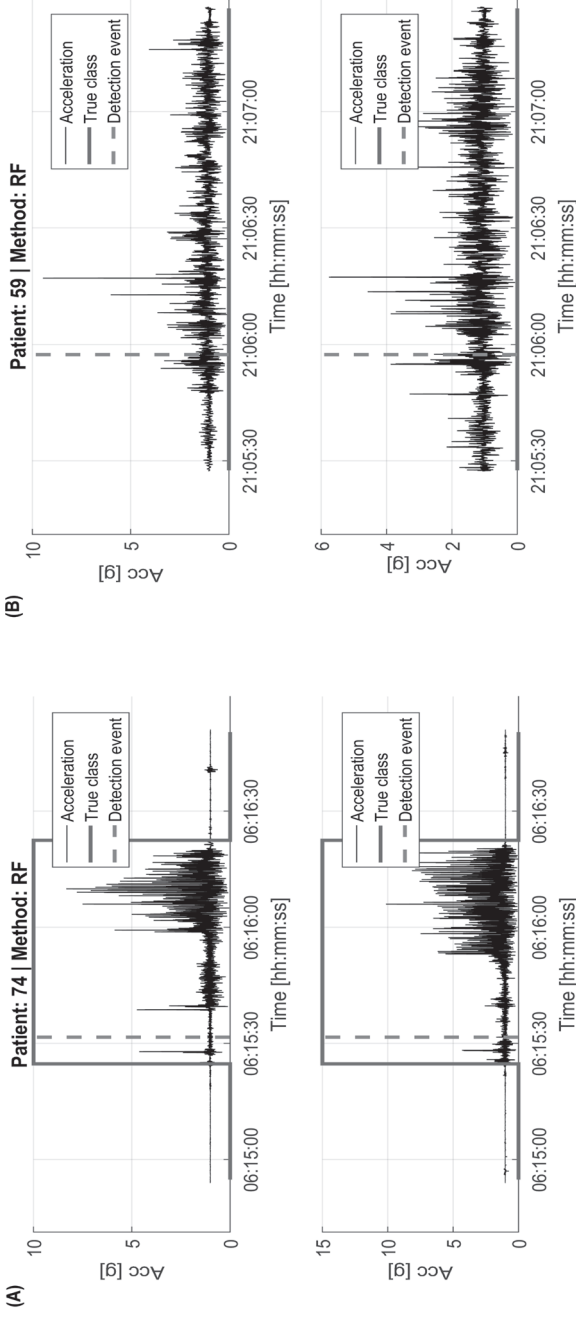
The classification algorithms that performed best in terms of sensitivity and false positive rate in the training data set, were KNN with 5 neighbors, SVM with linear kernel and RF with 30 trees. These three classification algorithms were further evaluated in the test data set (unseen data). In Paper II a true positive (TP) detection was considered if the time window contributing to the detection, contained at least one time instance labelled as a seizure (Paper II, Figure 2). Otherwise the detection was considered to be a false positive (FP). Seizures which generated no detection events were considered to be false negatives (FN). Sensitivity is calculated for an entire testing set by taking all patient data sets into account as an entity. Examples of true positive and false positive events are shown in Figure 6.

### **PD motor state recognition (Paper III-IV)**

The developed SVM model from the initial population sample was applied in Paper III to produce the TRIS index using the same features and principal components. In total 88 features were extracted and analyzed based on signals from each wrist sensor in the initial population sample to optimize the predictive performance of different classification algorithms. The SVM non-linear performed best in the initial population.<sup>104</sup> Two movement disorder specialists who rated clinical ratings in the initial study also rated patients in Paper III.<sup>103</sup>

The PKG objective summary scores BKS, DKS, FDS and percent time with tremor (09:00 – 18:00) that generated over the entire measurement period, were used to evaluate the effect of dose titration on objective measures in Paper IV. The PKG report contains a graphical representation of a median BKS and DKS over 6-day period, and it facilitates the detection of predictable motor fluctuations in relation to medication times. The report also contains graphical representations of the occurrence of tremor episodes and episodes of sleep-like immobility as well as a summary of time when the PKG is off-wrist.<sup>100</sup>

Blinded evaluation based on visual assessments of PKG graphs was conducted by two experienced movement disorder specialists to identify the presence of motor fluctuations in Paper III. The movement disorder specialists also assessed if there was a meaningful difference between PKG recordings before and after dose adjustment (Paper IV).



**Figure 6.** (A) An example of a TP event for patient ID 74 with estimated start of seizure. (B) An example of a FP event for patient ID 59 with estimated start of seizure. From research Paper II, with permission from the publisher.

### **Clinically relevant outcomes (Paper IV)**

The primary outcome of Paper IV was the change in global PD symptoms/signs as assessed by MDS-UPDRS subscale scores at the final visits compared to baseline. The secondary outcomes were the changes in the self-reported questionnaire including quality of life assessed using PDQ-8 and EQ-5D-5L, depression symptoms assessed using MADRS-S, non-motor symptoms assessed using NMS-Quest and wearing-off symptoms assessed using WOQ-19 from baseline to the final visit. The tertiary efficacy outcomes were the changes in self-reported questionnaires between baseline and the second visit and between the second and final visit, as well as the changes in objective scores derived from PKG recordings before and after dose adjustment.

### **Missing data and non-adherence**

Missing data and non-adherence of using sensors were summarized from Paper II-IV. Reasons for missing data were also explored with respect to technical errors or human related factors. The non-adherence data in Paper IV were extracted based on off-wrist time from the PKG reports. The first and last day of off-wrist time were excluded because the exact starting or finish time could not be determined. The percent of participants that were non-adherent was defined as the number of participants who removed the sensors more than 30% of at least one day divided by the total number of participants. The percent of non-adherence time was defined as the off-sensor time divided by the scheduled monitoring time.

# Results

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## End users' perceptions (Paper I)

Four categories emerged regarding perceptions towards the use of wearable technology based on the qualitative content analysis from focus group discussions: facilitators of sensor monitoring, barriers to monitoring, facilitators of usability and barriers to usability. Four categories and nine subcategories are presented in Table 4.

### Objective monitoring

The participants perceived potential benefits of using wearables where the information may facilitate the diagnostic process and disease treatment while being cost effective and decreasing the number of hospital visits. The participants considered that benefits gained from registration outweigh the possible inconvenience of use. They also emphasized the importance of interactive communication between patients and HPs before, during, and after monitoring.

The participants thought that unclear information might generate unnecessary questions, uncertainty and suspicion. The participants feared a lack of integrity and were worried about what information will be recorded and how and by whom this information will be used and interpreted. The participants were concerned about recordings with insufficient and invalid information or if the selected placement on the body was adequate for the purpose and whether enough variables were measured.

### Usability

The participants also described their perceived facilitators and barriers for using wearable technology in terms of design (e.g. color and material) and management (e.g. recharging batteries or taking the wearable on and off).

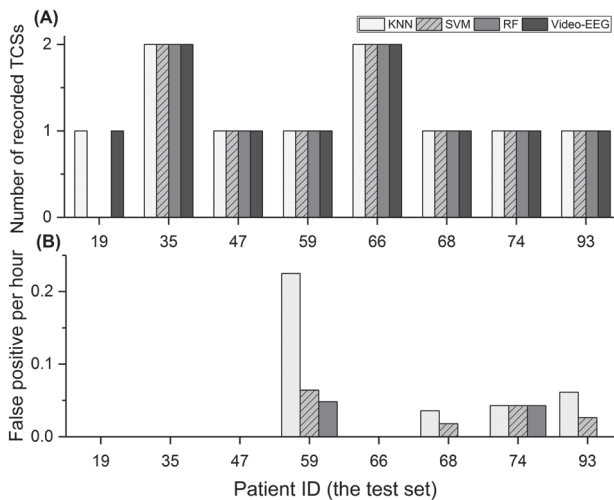
**Table 4.** Overview of categories and subcategories regarding sensor monitoring and usability.

	Categories	Subcategories
Objective monitoring	Facilitators of monitoring	Perceiving diagnostic and treatment benefits
		Valuing interactive information
	Barriers to monitoring	Perceiving unclear information
		Fearing lack of integrity
		Worrying about inconclusive recording
Usability	Facilitators of usability	Design that simplifies
		Management that simplifies
	Barriers to usability	Design that hinders
		Management that hinders

## Clinical evaluations (Paper II-IV)

### Tonic-clonic detection (Paper II)

In the training set, the K-nearest neighbors algorithm (KNN), support vector machine (SVM) and random forest (RF) all achieved 100% sensitivity and 0 false positive (FP) in detecting 27 TCSs in three patients. In the test set, the KNN detection algorithm detected all 10 TCSs in eight patients with 26 FPs (100% sensitivity, 0.05 FP/h, Figure 7). The SVM algorithm detected 9 out of 10 TCSs with 11 FPs (90% sensitivity, 0.02



**Figure 7.** Performance of the three classification algorithms in detecting TCS in patients of the test set. **(A)** Number of TCS detected by the three algorithms. **(B)** The average false positive rate per hour in each of the three classification algorithms. From research Paper II, with permission from the publisher.



FP/h, Figure 7), while the lowest false positive rate was obtained for the RF algorithm which also detected 9 out of 10 TCSs and only generated 6 FPs (90% sensitivity, 0.01 FP/h, Figure 7). Details of each classification algorithm performance for each individual in the test set are presented in Paper II, Supplementary Table 2.

## **PD motor state recognition (Paper III-IV)**

### **Instrumental testing (Paper III)**

Overall, the correlations between TRIS, TRS and UPDRS III items were decreased in Paper III when compared to the original study<sup>104</sup>. Compared to that, a lower correlation and higher root mean square error ( $r_s=0.23$ ,  $P<0.001$ , root mean square error RMSE=1.33) was found between TRIS and TRS in Paper III. A stronger and medium strength correlation between TRIS and TRS was found for participants who responded positively to a levodopa test dose and had unequivocal objective motor fluctuations ( $n=17$ ,  $r_s=0.38$  [medium strength 0.3 to 0.49],<sup>115</sup>  $P<0.001$ , RMSE= 1.29). Spearman correlation coefficients between TRIS, TRS and UPDRS III items were provided in Paper III Figure 1.

There were significant changes in clinical ratings and TRIS from practically defined *off* to *best on* state. TRIS was increased 0.32 from practically defined *off* to *best on* state ( $P=0.024$ ). TRS was also increased from a median of -2 to +1 when patients went from practically defined *off* to *best on* ( $P=0.001$ ). A median improvement of 3 points in UPDRS sum scores was found ( $P=0.001$ ).

### **Motor fluctuations based on PKG recordings**

The two movement disorder specialists agreed on 20 out of 25 patients including both with and without motor fluctuations. In five participants motor fluctuations were not detected in the PKG report.

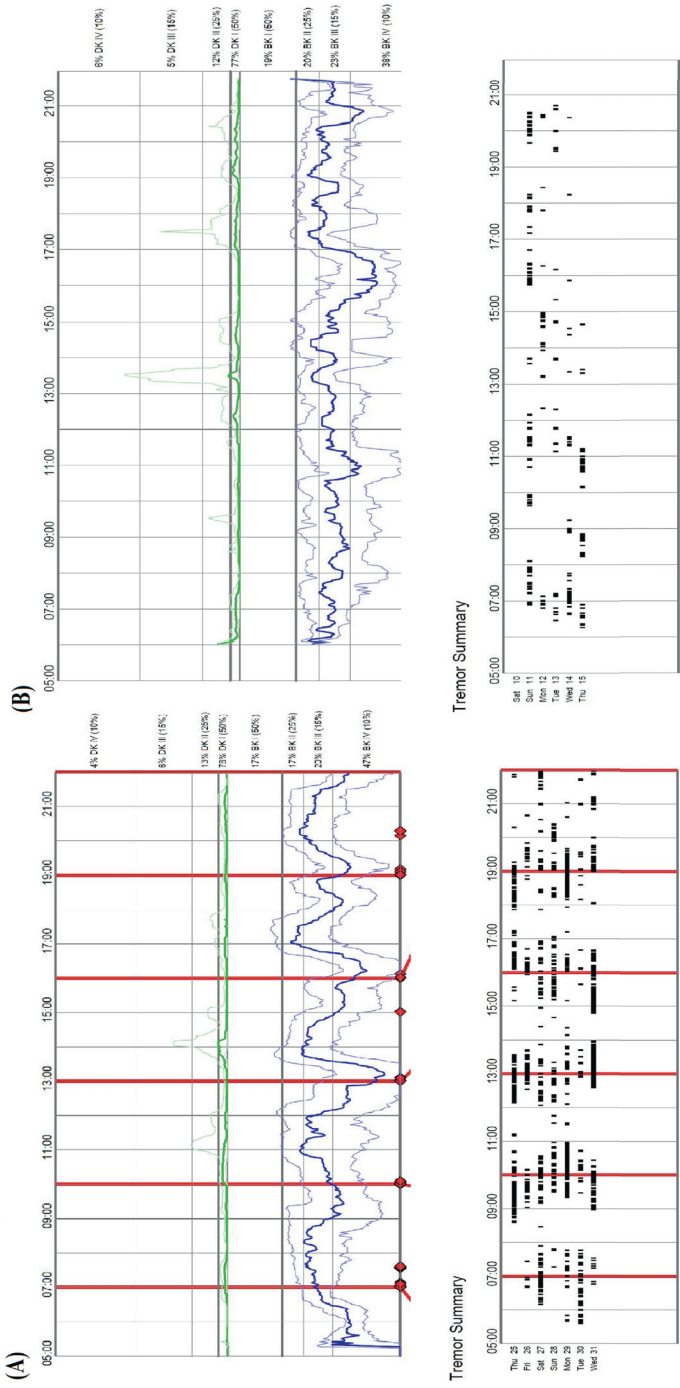
### **Individual dose titration (Paper IV)**

The mean levodopa-carbidopa dose was increased by 112 mg/day after dose adjustment (15%,  $P=0.001$ ) and the dose intervals were shortened from a mean of 173 to 151 minutes (12%). The introduction of LC-5 microtablets followed by a PKG-aided dose titration resulted in improvements in motor experiences of daily living (Part II) and motor examination (Part III) assessed using MDS-UPDRS (Paper IV, Figure 3).

There were no significant changes in non-motor experiences of daily living (part I) and motor complication (part IV) parts assessed using MDS-UPDRS. Health-related quality of life (measured by PDQ-8) significantly improved from baseline to the final visit. Self-reported symptoms included the number of non-motor symptoms (NMS Quest), the number of wearing-off symptoms (WOQ-19) as well as the number of depressive symptoms (MADRS-S), which were significantly decreased from baseline to the final visit. There was no significant change in the number of symptoms improving after the next dose in WOQ-19. Generic quality of life, as measured by EQ-5D-5L scores, did not change over the study period (Paper IV, Table 3). There were no significant changes in PKG objective summary scores in BKG, DKS, FDS and percent daytime with tremor from the first measurement period to the second period (Paper IV, Table 3).

### **Blinded clinical evaluations of PKG**

PKG reports from 20 patients had sufficient data for evaluation by the specialists before and after dose adjustments. Of these 20 patients, 12 patients (60%) showed improvement of bradykinesia without appearance of pronounced dyskinesia after dose adjustment, three patients did not change and in five patients (25%) the PKG-recordings indicated deteriorated motor features. An example of a patient's PKG reports before and after dose adjustment is shown in Figure 8.



**Figure 8.** An example of evident wearing-off phenomena shown in the PKG graph before dose adjustment. The bold blue line represents the median of bradykinesia scores and the bold green line represents dyskinesia scores for every 2 min of the 6-day period of the PKG measurement. The thin blue lines indicate the 25<sup>th</sup> and 75<sup>th</sup> percentiles of bradykinesia scores. The thin green line represents the 25<sup>th</sup> and 75<sup>th</sup> percentiles of dyskinesia scores. The vertical redlines indicate prescribed dose intake times. The black raster patterns represent the timing of tremor episodes. The median of bradykinesia score was improved (smoother in the blue line) without increasing the median of dyskinesia (the green line) after dose adjustment. From research Paper IV, with permission from the publisher.

## Missing data and non-adherence (Paper II-IV)

Missing data attributed to either technical errors or human factors (e.g. incorrectly starting the sensors) are presented in Table 5. Non-adherence to wearables has been reported in Paper II and IV. There were three PwE (4%) who took off the sensors due to discomfort (Paper II). Eleven PwPD (44%) took off the PKG device for more than 30% of the time in one day during two monitoring periods (Paper IV). The median percentage of non-adherence time during the sensor monitoring among PwE those who took off the sensors (n=3) was 49.7%, and for PwPD (n=11) was 14% for both periods.

**Table 5.** Overview of missing data in each corresponding setting for Paper II-IV.

	Paper II n=75	Paper III n=25	Paper IV n=25 <sup>a</sup>
<b>Setting</b>	Hospital	Lab	Free-living
<b>Wearables</b>	Shimmers3	Shimmers3	PKG
<b>Total monitoring time, hours</b>	8933	104.3	6912 <sup>b</sup>
<b>Missing data, hours (%)</b>	1952 (22)	3.7 (3.5)	331 (4.8)
Technical errors	Synchronization between sensors, battery failure or data storage problems	Synchronization between sensors	NA
Other reasons	Sensors were not correctly started	None	Off-wrist
<b>Percent of total adherence time, %</b>	97.9	100	95.2
<b>Percent of participants with non-adherence</b>			
Female n (%)	3 (6)	0 (0)	2 (20)
Male n (%)	0 (0)	0 (0)	9 (60)
<b>Percent of non-adherence time, %</b>			
Median (range)	49.7 (49-50)	0 (0)	First period 14 (7-78) Second period 14 (7-60)

<sup>a</sup> There were 25 participants who completed two periods of PKG monitoring and 24 participants completed the study.

<sup>b</sup> Scheduled monitoring time, due to the difficulty to determine when participants start or stop the measurements.

# Discussion

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This thesis covers several aspects of the possible use of wearables in clinical applications for monitoring epilepsy and PD, namely perspectives from end users, feasibility from practical experiences and clinical evaluation of algorithm performance as well as early attempts to assess clinical effects of monitoring using wearables.

The description and identification of barriers and facilitators adds to the knowledge of clinical implementation of wearables to enable long-term use from both patients and health professionals' perspectives (Paper I). The proposed algorithm in detecting TCS achieved a high sensitivity and a low false positive rate (Paper II). Wearable sensors can be used to quantify motor states in PD both in instrumental testing (Paper III) and in passive movement monitoring (Paper IV). Wearables can be applied as tools to ascertain seizure frequency in epilepsy and to monitor treatment effects in PD. The information provided by the commercial proprietary algorithm is feasible for individual dose titration in PD (Paper IV). The PD motor and non-motor symptoms, disease specific quality of life, number of wearing-off symptoms as well as depression symptoms improved after dose titration. The adherence to using wearables is high. Technical stability requires further improvement due to missing data attributable to technical errors (Paper II-III).

## The methodological considerations

### End users' perceptions

The involvement of end users increases their engagement in using wearables by having an influence on the design of their own devices. The main advantage of focus groups is to gather large amounts of data through the dynamic group interaction on a specific topic of interest within a limited time.<sup>116</sup> Focus groups make it possible for the participants to explore and clarify their views that might be left underdeveloped in an interview.<sup>117</sup> Homogeneity and heterogeneity sampling in age, gender, functioning level, and previous experience of wearables allow a rich source of data to ensure credibility and also facilitate transferability to a larger context. The trustworthiness of categories and subcategories was strengthened by continued discussion among all authors of Paper I.<sup>99</sup>

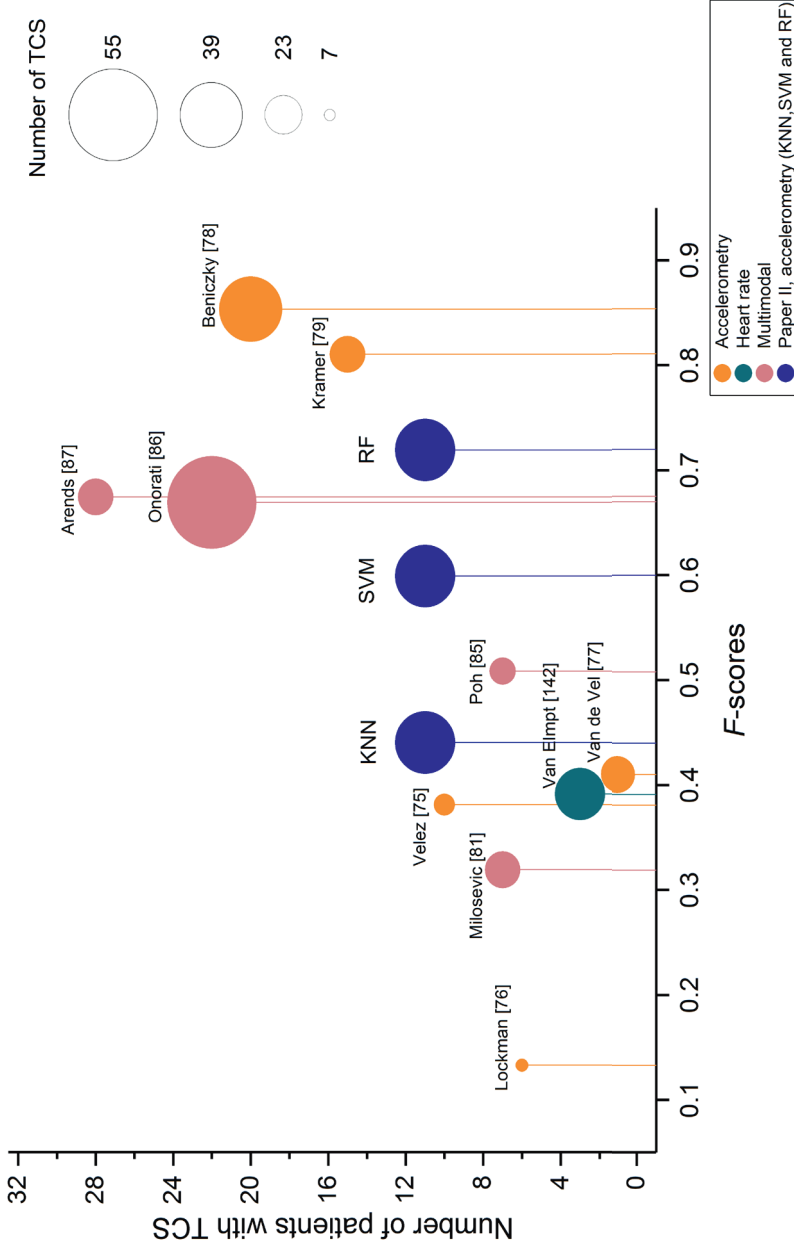
Individuals with severe epilepsy or PD were not included in Paper I. People with severe epilepsy or PD may experience more difficulties with usage. However, they are a group that may gain more benefits from using objective monitoring. Individual interviews can be conducted with people with severe epilepsy or PD to further identify specific problems or difficulties with use.

### **Tonic-clonic seizure detection**

Paper II showed comparable sensitivity and false positive rate (RF 90% sensitivity, 0.01 FP/h) with an algorithm based on only one accelerometry modality, compared to multimodal systems for TCS detection (Figure 9). *F*-score has previously been proposed as an appropriate approach to compare different seizure reporting technologies and is the weighted mean between sensitivity and precision.<sup>33</sup> *F*-scores of different TCS detection devices are presented in Figure 9.

There are two accelerometry-based commercially available devices reporting similar sensitivity (around 90%) and false positive rate (around 0.01/h) for TCS detection. One is a wrist-worn device (EpiLert, Israel) which detected 20 out of 22 seizures including tonic and tonic-clonic seizures in 15 patients (sensitivity 91%, 0.005 FP/h).<sup>79</sup> In that study<sup>79</sup> patients with seizure-like movements were excluded (e.g. patients with dystonic posturing, subtle behavioral automatisms and suspected psychogenic non-epileptic seizures). Another accelerometry-based device detected 35 out of 39 TCSs in 20 patients (sensitivity 90%, 0.008 FP/h).<sup>78</sup> In that study<sup>78</sup> patients were instructed to refrain from performing repetitive daily movements that could be mischaracterized as a seizure (such as brushing teeth using the hand that had a sensor attached). The algorithm development was not described in detail in these two studies.

The algorithm performance in Paper II was achieved without inclusion bias. Inclusion bias refers to the use of training and test data sets from the same patients in the algorithm development. This definition of inclusion bias has recently been proposed in a review<sup>118</sup> where it was emphasized that a strict separation of training and test populations is necessary for unbiased performance evaluation. Inclusion bias may lead to potential overfitting in that the algorithm obtaining a good performance in the training data set fails to generalize to a test data set (i.e. unseen data). The training and test data must be stratified, which means that the entire data set recorded for any one patient (including all the seizures recorded for that individual) should be assigned either to the training or test set.



**Figure 9.**  $F$ -score of each study with corresponding modality for TCS detection is presented and mapped with number of TCS included in the study.  $F$ -scores were calculated as a weighted mean between sensitivity and precision [ $F$ -scores =  $2 \times (\text{sensitivity} \times \text{precision}) / (\text{sensitivity} + \text{precision})$ ] of detection performance in order to conduct a standardized comparison with other seizure reporting technology, proposed by Bidwell et al.<sup>33</sup>  $F$ -score is a continuous scale ranging from 0 to 1 where higher indicates better performance.

Among the studies in Figure 9, only a few<sup>84,87</sup> had a separate training and test population used for algorithm developments and evaluations, and most proprietary algorithms were not presented in detail in the studies. A multimodal system (Nightwatch, Netherlands) based on the combination of accelerometry and heart rate for detecting all convulsive seizures achieved a comparable sensitivity of 86% with 0.004 FP/h, without inclusion bias.<sup>87</sup>

### **PD motor state recognition and dose titration**

Weaker but significant correlations between the objective sensor index TRIS and clinical ratings were found in the new independent population (Paper III). It is common that correlations are weaker when an algorithm that is trained on a specific population is tested in a new population. The reason can be over- or under training of the algorithm, but a difference between the populations can also contribute. The decreased correlation was therefore expected. The algorithm performance is nevertheless robust in the sense that it describes motor symptom features that are responsive to levodopa in the new population.

Several studies<sup>119-122</sup> demonstrated a high correlation ( $r= 0.73$  to  $0.9$ ) between sensor-based objective measures and the corresponding UPDRS III sub-scores (e.g. finger tapping) for assessing bradykinesia during a single instrumental task. The TRIS was developed to map on the TRS scale that incorporates the global motor response rather than any single or sum of UPDRS items. The attempt of developing the sensor-based index is to provide more objective measures for detecting different PD motor states and use it for constructing individual dose-response models rather than to replace existing clinical rating scales or develop a sensor-based version of clinical ratings. Therefore, a “perfect” correlation between objective measures and clinical ratings is not necessary for a simple quantitative agreement and subjective ratings.<sup>123</sup>

Dose adjustments based on PKG recordings resulted in significant improvements in motor and non-motor PD symptoms without increased dyskinesia in short term. Although the value of the finding is somewhat limited by the open-label observational design, the use of wrist-worn sensors is feasible to adjust treatment through monitoring movement profiles. Overall, 12 out of 20 patients showed a better motor profile after dose titration based on PKG measurements, but none of the PKG summary scores showed significant improvement. It appears that clinical interpretation of PKG reports is more sensitive to change than PKG



summary scores. The responsiveness of PKG objective scores remains to be examined.

### **Instrumental testing versus passive monitoring in PD**

Both Paper III and IV used an accelerometry-based device to quantify bradykinesia and dyskinesia. Paper III used features based on a repeated pronation-supination movement conducted in a laboratory and Paper IV used movement monitoring in a natural everyday environment. The instrumental testing with a single motor task might be sufficient enough to capture changes in motor dynamics that reflect different motor states. However, the requirement for patients to conduct repeated tests can generate compliance issues whereas passive monitoring requires fewer or no inputs from patients. Also, one potential drawback for instrumental testing is that most patients tend to perform better during clinical assessments than in their daily environment, which can make it difficult to evaluate if the results from the instrumental testing will actually reflect their treatment effects. Passive monitoring, such as the PKG device, can provide the day-to-day variations of movement.

### **Machine learning algorithms for monitoring epilepsy and PD**

The implementation of machine learning in clinical care is not straight forward. Challenges regarding data quality, large data management and the clinical and biological relevance of the algorithm models<sup>124</sup> are also found in other medical disciplines where machine learning is applied e.g. myocardial infarction diagnosis<sup>125,126</sup> or image classification in radiology.<sup>127</sup>

Large data sets can lead to difficulty in condensing the collected information and extracting the relevant target parameters.<sup>91</sup> Although machine learning algorithms are robust enough to handle large-scale data,<sup>128,129</sup> the algorithms generally don't supply explanatory power.<sup>130</sup> With high-dimensional wearable data, there is limited utility to fully understand the behavior of the black boxes.<sup>130</sup> When an algorithm is to be used to produce a substitute measure for medical decision support it is imperative that the logical connection between the phenomenon and the algorithm outcome is transparent.<sup>130</sup> The understanding probably needs to precede data collection, by determining what will be the most clinically relevant and measurable features. Therefore, communication between health professionals, engineers and patients is important to address unresolved clin-

ical issues and choose the clinically most prioritized parameters to be measured in wearables.

The challenge when developing algorithms usually involves the difficulty to obtain a good-fit model without overfitting or underfitting.<sup>130</sup> Overfitting is more common and is usually due to the complexity of the model or too much noise in the training data. To some extent, a tradeoff between the model complexity and the possibility of overfitting needs to be considered. When the number of training samples is low a complex model is likely to result in overfitting and poor generalization. In Paper III the initial training sample was dominated by TRS -2 to +1 values and in the new test sample a large proportion of the observations was observed at the more extreme TRS values (i.e. severe Parkinsonism or “on” with moderate to severe dyskinesia). As only few extreme TRS values were present in the training sample, the algorithm cannot make accurate predictions in the extremes of the TRS and the algorithm therefore underestimated Parkinsonism when TRS values were lower than or equal to -2. More data with a higher prevalence of severe Parkinsonism and severe dyskinesia would help to re-train the predictive algorithm and would be useful to improve its generalizability.

For tonic-clonic seizure detection, a variation in the number of FPs was noted between individuals in relation to heterogeneous motor phenomena of TCSs (Paper II). To improve the algorithm performance and reduce FPs, patient-specific algorithms are suggested.<sup>131</sup> More data from each patient is also required to construct a reliable patient-specific algorithm. Although the present system is not primarily focused on real-time analysis, the SVM model is expected to be the most computationally inexpensive for commercializing wearables. The generalization to multimodal systems may also be more suitable in some of the proposed algorithm models than others. However, more data is still needed to propose the future strategy for development of wearables.

Limited data is a common issue in the field.<sup>130,132</sup> Data sharing between different projects that are working in the same direction would enable algorithm development to move forward regarding clinical use in epilepsy and PD. Sampling methods, feature extraction and validation methods should be provided in study reports. Releasing the associated code for the model building in the public domains would allow reproduction in confirming studies. For example, in clinical applications of machine learning

in cardiovascular disease, the continued development and refinement of algorithms was largely attributed to public ECG databases.<sup>124</sup>

### **Missing data and non-adherence**

One main technical problem occurring in our studies is missing data. Five TCSs were unrecorded by sensors in Paper II due to technical errors and the missing data was mainly attributable to technical failure. The amount of missing data needs to be kept in mind even in the development phase, especially as it may have an impact on the performance when the system is converted to real-time seizure detection. PD motor symptoms involve movement characteristics that change progressively over time, and a real-time system continuously measuring relevant features over one to two weeks might be less sensitive to missing data. Apart from technical problems of the sensors, there were several practical issues, such as a complicated process to start and stop the sensor monitoring. This led to difficulties for health professionals who were not familiar with the technical instruments and also reflects that the system is not yet mature. It indirectly led to missing data attributed to human factors. The system needs to be simple to operate and adapt to a level where technical knowledge should not be unnecessarily demanding. It is important that health professionals and technicians work closely together to address technical difficulties and clinical needs to improve the usability.

## **Limitations**

One limitation of using focus group discussions (Paper I) is that it might hinder the expression of opposed viewpoints during the group discussions. The high dynamic of interaction might also suppress the development of alternative ideas from individuals who were not actively participating. The moderator and the assistant moderator ensured a relaxed and open environment to allow different expressions from all participants during the group discussions.

One limitation across Paper II-IV was that the number of participants was relatively low. However, as proof-of-concept studies, it is reasonable that a small number of participants but saturated data, is needed prior to larger clinical trials to test and develop the design of the algorithms. Paper IV was an observation open-label design with a limited follow up time and

no comparison group. A placebo effect is likely to contribute to some extent to the study findings in Paper IV.

## **Clinical implications**

### **Tonic-clonic seizure detection**

Paper II achieved a low FP rate using only one modality. Using one modality requires less power than a multimodal system. An increase of the expected battery life facilitates long-term use of the proposed accelerometry-based system for TCS detection. Including high frequency movements of normal daily activities in the training algorithm may help to reduce FP rates and thereby achieve a more robust system for measuring TCS frequency also in a natural setting.

Most non-invasive seizure detection devices have achieved false positive rates around 0.2 FP/24 hours which is too high for clinical use. A majority of patients would nonetheless accept false positives as long as they are fewer in number than the correct detections.<sup>65</sup> An acceptable rate (i.e. 1 FP for every 3 TP<sup>133</sup>) is dependent on the seizure frequency in a given individual, and it cannot be directly translated into FP/h rate of the detection algorithm. Reducing FP/h of TCS detection can provide a more reliable seizure count and reduce anxiety for patients and caregivers regarding seizures they are unaware of. FP reduction could make seizure alarm systems more robust. Reliable information on TCS seizure counts is needed to optimize pharmacological treatment so that the seizures can be prevented or reduced and eventually lead to a normal lifestyle being maintained in PwE.<sup>118</sup>

### **Individual dose-response models and dosing suggestions in PD**

The development of treatment related motor complications is a major clinical problem in PD. Paper III demonstrated that, in the new population, the previously developed algorithm performed best in PD patients with a positive response to levodopa and clear motor fluctuations. The population in Paper III was selected based on prescription records, not on the reported occurrence of symptom fluctuations. It confirms the clinical usefulness of applying the method to the specific group of patients with undeniable levodopa response and short effect duration.

Individual dose-response models based on TRIS were developed for providing individual dosing suggestions in terms of the maintenance dose

and morning dose.<sup>104,134</sup> In Paper III individual dose-response models could be fitted to 76% of the study population. Dosing suggestions based on TRIS were found to be significantly correlated with the dose adjustments chosen by the responsible physician in Paper IV.<sup>135</sup> Automated objective interpretation of sensor-based measurements and individualized dose suggestions could, in the long run, improve PD symptoms and thereby improve quality of life in PwPD. If integrated with other remote platforms (e.g. web or mobile), it will allow remote assessments when patients are in their home environment, and it may be possible to decrease the amount of hospital visits. This would be helpful for PwPD who live in rural areas.<sup>136,137</sup>

Objective measurements are the most valuable when there is a therapy that influences the measured disease indicator.<sup>90</sup> Paper IV showed a feasible approach to optimization of oral levodopa medication for short term pharmacological management of PD and improved disease-related quality of life in PwPD. The passive monitoring facilitates an early detection of untreated bradykinesia and unrecognized motor complications when patients are not aware of them themselves or find them difficult to describe. Early detection of motor fluctuations may facilitate stabilization of the treatment and improve clinical outcomes.

Most PwPD in Paper IV showed a need for dose adjustments based on PKG recordings, but some of the patients did not experience any burdensome symptoms due to undermedication according to their self-descriptions. PKG recordings could both underestimate and overestimate symptoms and symptom fluctuations. It is therefore necessary to confirm the results in clinical interviews. This is a problem shared with probably all home or free-living assessments, including long term ECG and diaries. In Paper IV the impressions of dose effect duration and dose efficacies derived from the PKG were discussed with the patients in the same way that the PKG-information is used in clinical practice, i.e. as an information tool and a pedagogical tool.

Wearables with integrated reminders may also facilitate adherence to medication intake. This may mitigate the difficulty to manage multiple doses per day and help avoid motor fluctuations due to poor medication compliance. The medication adherence in Paper IV is very high in almost all participants compared to other previous studies.<sup>138,139</sup>

While wearables can be useful to quantify treatment effects in PD, they can also facilitate the identification of PwPD who may require adjusting

treatments like deep brain stimulation (DBS). The presence of dyskinesia or the onset of motor fluctuations sensed by wearables might be used to inform an adaptive DBS device which adjusts the stimulation based on the sensor data. Such feedback closed-loop stimulation might improve the efficacy of DBS and decrease the battery consumption. However, the performance of wearables for measuring PD motor symptoms has to improve substantially in order to be feasible for such application.

## **Wearable system considerations**

### **Adherence to wearables**

Adherence to wearables was high across Papers II-IV. The high adherence reflects a positive acceptance towards the use of wearables, as perceived by the end users who saw possible benefits and valued the benefits more than the possible inconveniences (Paper I). Although there were 11 participants who took off the PKG device for more than 30% of the time in one day with only one sensor used, the total adherence time (95.2 %) of two monitoring periods remains high. The adherence time in Paper IV was in line with a study that reported 7-day adherence to wearables in PwPD.<sup>140</sup> The reason for non-adherence could be that the participants had to manage other technical devices in parallel during the study (Paper IV). Three PwE took off the sensors due to discomfort (Paper II), and that non-adherence might be related to the design of the sensors.

### **Is a single wrist-worn sensor enough?**

A single wrist-worn sensor is easier to use for patients from a practical perspective. Signals from one wrist-worn sensor are probably sufficient in detecting TCSs in epilepsy and monitoring motor symptoms in PD. However, one single sensor might not be satisfactory in detecting other seizure types, for example hypermotor seizures.<sup>141</sup> Also, the use of a single sensor could be difficult when the motor manifestation is unclear as to which wrist is predominant, or to classify activities that could be mistaken for disease related features. The use of bilateral sensors has some potential advantages to avoid misinterpretation of daily activities, e.g. brushing teeth or whipping cream with the hand that the sensor is attached to which might be misclassified as a seizure.<sup>78</sup>

## Integrity issues

The concerns of privacy regarding the gathering of information using technology have been raised in the past decades. PwE and PwPD stressed that the privacy of the data must be ensured and only relevant professionals should have access to the data (Paper I). Most participants were concerned if their daily activities could be discerned from the data collected by wearables (Paper I). The possible privacy issues can be more challenging when patients have cognitive impairment or if they are particularly suspicious which might be a side effect of the medication in PD.<sup>2</sup> A recent review suggested that the data collected by wearables should be secured by regulatory means through legal obligations.<sup>91</sup> The recently released GDPR legislation addresses similar privacy concerns by ensuring that personal data belongs to the person under legal obligations. The regulation facilitates the protection of privacy on collected data being used by a third party.

### An “all-in-one” device or one size fits no one?

The portrayed perceptions from Paper I call for an “all-in-one” device. The participants perceived that wearables can be used to detect disease symptoms including non-convulsive seizures and PD non-motor symptoms while retaining the feature of being easy to use. Technically realistic solutions and these perceptions may be difficult to match. The use of a multimodal system can detect more variables than accelerometry, but it substantially increases the power consumption and data management. A more burdensome battery might then have to be used. A multimodal system may not be necessary for every patient, e.g. for persons who have dominant PD motor symptoms without reported non-motor symptoms after screening, it will be effective to use only one accelerometry modality in monitoring motor symptoms to improve treatment effects. Also, there are related ethical issues for collecting data that actually will not be used.

A conflict in perception emerged from the focus group discussions. The participants perceived the use of wearables as a cost-effective tool to monitor disease symptoms as well as to improve disease management while information exchange between patients and health professionals was expected to be sufficient. Information exchange before, during and after monitoring or even a wish for rapid and immediate feedback from sensors was emphasized by both patient groups. The perception of requiring intensive information exchange might be caused by concerns and worries of using a new wearable technology where patients need confir-

mation and support during use. In a recent review,<sup>2</sup> experiences of using wearable technology in epilepsy, PD and stroke were synthesized, and the lack of confidence in handling the new wearable technology emerged as a main theme. The desired information exchange requires extra human resources to communicate and deliver sufficient feedback and support, which is still an unmet need when it comes to responsibility for how to provide real-time feedback while avoiding an extra burden for both patients and health professionals. In reality, the use of wearable sensors might not be as cost-effective as hoped for, since substantial resources for technical development and clinical validation are needed in its' initial stage. Using wearables for symptom monitoring in a clinical context implies both opportunities and challenges.

### **Opportunities**

- Continuous and objective monitoring
- Feasible in home environment for long term use
- Potential to follow-up treatment effects and support decision making through monitoring related variables of epilepsy and PD
- Further applications incorporated with other platforms, e.g. web-application, closed-loop feedback system
- Monitoring individual variability in a standardized approach
- High user acceptance

### **Challenges**

- Large resources are demanded in the initial stage of developing the technology
- Privacy concerns
- Demands for battery consumption
- Large data management
- Technical requirements for multimodal system
- Data quality issues
- Clinimetric validations in a large sample population



# Conclusions

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- The use of wearables as an objective tool to improve disease management in patients with epilepsy and PD showed both opportunities and challenges.
- Facilitators and barriers perceived by end users are important to consider in the design of wearables to facilitate long term use.
- The developed algorithms performed well for tonic-clonic seizure detection in epilepsy and motor state recognition in PD using wearable sensors.
- The use of wearable-derived information for individual dose adjustment in PwPD improved PD motor and non-motor symptoms as well as health-related quality of life in the short term.

# Ongoing studies and future perspectives

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The knowledge provided by these studies will be the basis for further work to develop a multimodal system by incorporating more physiological measures to improve detection performance for monitoring epilepsy and PD.

In epilepsy the monitoring of heart rate and oxygen saturation has previously shown to be useful in detecting tonic-clonic seizures (TCSs).<sup>84,142,143</sup> The monitoring of movement and more physiological variables using the multimodal garment may further reduce the number of FPs and improve the TCS detection performance. A multimodal system carries the potential to register physiological events that precede TCSs and also to record postictal physiological changes. This is a prerequisite for identifying PwE who might be at risk for sudden unexpected death in epilepsy (SUDEP) and develop interventions which might prevent SUDEP and eventually be lifesaving.<sup>144</sup>

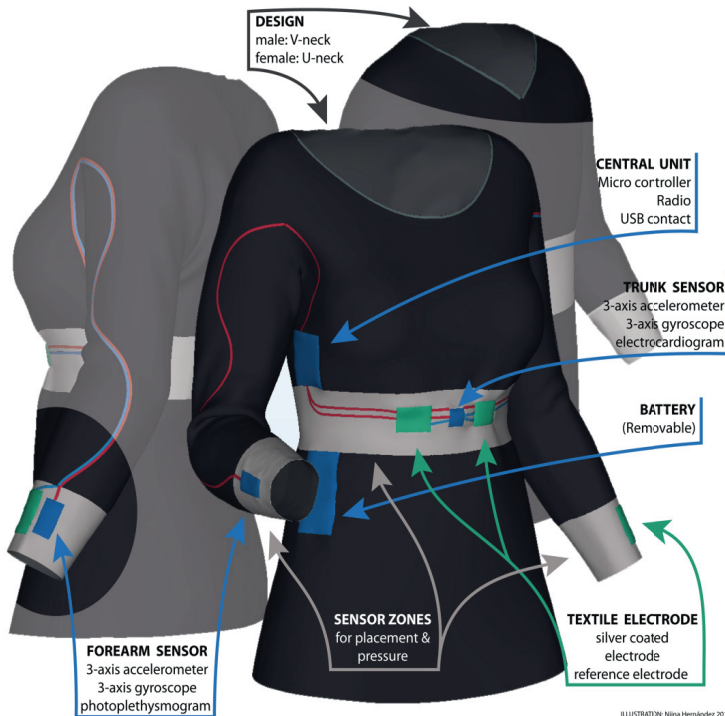
Non-motor fluctuations might be visible through monitoring of one or more physiological variables. A majority of PwPD will develop dysautonomia as the disease progresses. Orthostatic hypotension is a common non-motor symptom resulting from cardiac dysautonomia which occurs during a change of position from sitting or lying down to standing and it can potentially lead to falls in PwPD.<sup>145</sup> The monitoring of blood pressure using continuous and objective measurements has a potential to detect cardiac dysautonomia by providing more subtle measures than traditional intermittent methods of measuring blood pressure.<sup>146,147</sup> The clinical application of using pulse transit time (PTT) to evaluate changes in blood pressure in PwPD will be examined. The relationship between PTT and non-motor symptoms that is self-assessed by PwPD using a mobile application in relation to the medication intake time is further explored.

## Further integration – a multimodal integrated garment

The multidisciplinary wearITmed consortium is a platform for collaboration of researchers from medicine, engineering, textile and material science aiming to develop garment integrated multimodal sensors that can

be applied for clinical use in epilepsy, PD and stroke.<sup>92</sup> The multidisciplinary approach allows cross-scientific knowledge to be involved at an early stage to develop a clinically relevant system that fulfills the need of end users while sustaining realistic technical and practical solutions for long-term use. The use of the garment with integrated multiple sensors aims to measure movement and physiological variables like heart rate variability, electrodermal activity, changes in blood pressure and oxygen saturation.<sup>92</sup> These variables were considered the most clinically relevant for symptom monitoring.

The multimodal integrated garment contains three sensor zones, and each zone incorporates an SD memory card to store data for off-line analysis. Illustration of the garment with integrated multiple sensors is shown in Figure 10. Inertial sensors include three-axis accelerometers and three-axis gyroscopes integrated in all three zones. Optical sensors like photo-



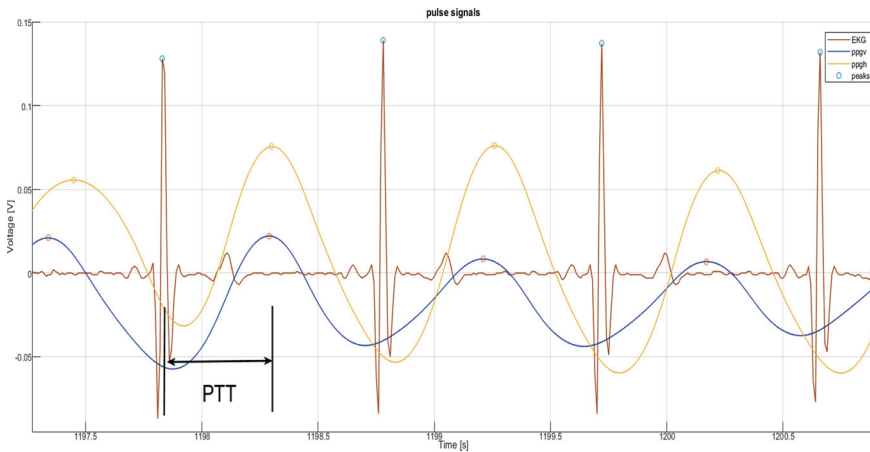
**Figure 10.** An example of a 3D-model of the garment design and different components integrated in the garment. Reprinted with permission of BioMed Central from “An upper body garment with integrated sensors for people with neurological disorders – early development and evaluation.” by M. Alt Murphy, F. Bergquist and B. Hagström et al., 2019, *BMC Biomedical Engineering*, 1:3. © by Springer Nature, Switzerland AG 2019, Alt Murphy et al,<sup>92</sup> Fig.2

plethysmography (PPG) are integrated in both forearm sensor units and two textile silver coated electrodes for heart rate registration are integrated in the trunk sensor zone.

### Physiological measures

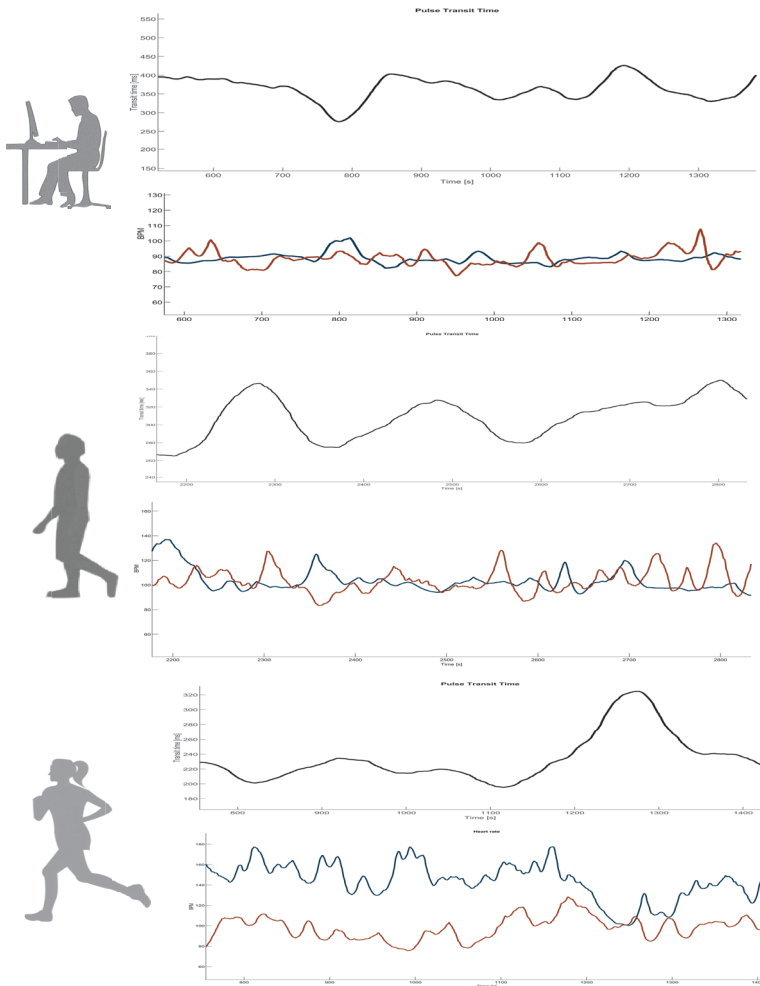
Photoplethysmograph (PPG) is an optical technology that measures blood volume changes in the peripheral circulation through light transmission or reflection. PPG can be used to measure pulses radiating to the periphery with each heartbeat.<sup>148</sup> A pulse oximeter with a built-in PPG sensor measures oxygen saturation based on the theory of different spectral properties of Hb and HbO<sub>2</sub>.<sup>149</sup> Pulse rate variability detected from PPG is significantly correlated with the HRV derived from an electrocardiograph (ECG).<sup>150,151</sup>

Pulse transit time (PTT) is usually calculated as the time interval from the R-wave peak on the ECG to the arrival of the maximum peak of the pulse wave in the PPG signal to measure pulse velocity in a continuous fashion. The PTT reflects the time taken for the pulse pressure wave, created by the blood ejected from the heart to the aorta, to travel to the periphery.<sup>152</sup> Factors that influence PTT include blood pressure and the autonomic regulation of the vascular wall tension, which modulates the stiffness of the arteries. The pulse wave travels faster in a stiff vessel resulting in a shorter PTT.<sup>153</sup> In theory PTT should be inversely proportional to the blood pressure. However, different studies show heterogeneous results regarding the correlation between beat-to-beat PTT and systolic blood



**Figure 11.** An example of PPG signal and ECG signal (the red line) collected from a multimodal sensor garment. PTT is calculated as the interval between R wave peaks and the maximum peaks of PPG. The blue line indicates the PPG signal collected from the left optical sensor. The yellow line indicates the PPG signal collected from the right optical sensor.

pressure as well as diastolic blood pressure measured by a cuff-based blood pressure monitor.<sup>154,155</sup> The relationship between PTT and blood pressure may highly vary among individuals. PTT is also influenced by other factors such as oxygen saturation and thoracic pressure. PTT has been used as an indirect marker reflecting autonomic imbalance in obstructive sleep apnoea syndrome and cardiovascular reactivity predicting cardiovascular disease.<sup>156-158</sup> An illustration of PTT is shown in Figure 11. Examples of pulse transit time and heart rate based on ECG and PPG signals derived from the garment during sitting, walking and running activities are shown in Figure 12.



**Figure 12.** Examples of continuous measurements of pulse transit time and heart rate derived from the garment with integrated multiple sensors during sitting, walking and running. The black lines indicate the continuous measurement of PTT. The blue lines indicate heart rate derived from the ECG signal, and the red lines represent heart rate derived from the PPG signal.

## Evaluation of the garment integrated multimodal sensors

The development of the garment has a strong focus on the end users' needs and preferences. The results obtained from the focus group study (Paper I) were incorporated into the garment design. An evaluation of each prototype is also conducted with individual interviews and questionnaires and the feedback from individual experiences was further integrated into the development of the next prototype. PwE or PwPD might find it easier to manage one garment with integrated multimodal sensors compare to multiple separate sensor units. The daily impact on the quality of life in long-term use of wearables will also be explored along with if the use of wearables improves user engagement in disease monitoring.

All integrated electronics are washable except for the battery to facilitate the usability for long-term use. Battery recharge is required one time per 24 hours. The technical tolerability for long-term use is desirable to be followed.

The algorithm performance for detecting motor seizures in epilepsy and motor states in PD is evaluated in parallel with the garment development and evaluation. The algorithm development in epilepsy will also focus on the detection of other motor seizure types such as hypermotor seizures or psychogenic non-epileptic seizures. An automated algorithm for analyzing PTT and heart rate variability measured by the multimodal garment will be developed. Generalized algorithms may be further developed to adapt to a multimodal system for monitoring epilepsy and PD.

Overall, large sample sizes and data are needed. The external validity for translating the algorithm performance of seizure detection from a hospital to a free-living environment needs to be further explored. Randomized controlled studies may eventually be possible when wearables have been proven "good enough" to provide clinically relevant information in epilepsy and PD. Interventional studies over a longer period are desirable to confirm that the objectively measured indicator can support therapeutic effects in epilepsy and PD.

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# References

1. World Health Organization. Neurological disorders public health challenges. *WHO Library Cataloguing-in-Publication Data* 2006.
2. Johansson D, Malmgren K, Alt Murphy M. Wearable sensors for clinical applications in epilepsy, Parkinson's disease, and stroke: a mixed-methods systematic review. *J Neurol* 2018; **265**(8): 1740-52.
3. Feigin VL, Abajobir AA, Abate KH, et al. Global, regional, and national burden of neurological disorders during 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet Neurology* 2017; **16**(11): 877-97.
4. Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy. *Neurology* 2017; **88**(3): 296.
5. Schmidt D, Schachter SC. Drug treatment of epilepsy in adults. *Bmj* 2014; **348**: g254.
6. Forsgren L, Beghi E, Oun A, Sillanpaa M. The epidemiology of epilepsy in Europe - a systematic review. *Eur J Neurol* 2005; **12**(4): 245-53.
7. Osorio I, Manly BFJ. Probability of detection of clinical seizures using heart rate changes. *Seizure* 2015; **30**: 120-3.
8. Bateman LM, Li C-S, Seyal M. Ictal hypoxemia in localization-related epilepsy: analysis of incidence, severity and risk factors. *Brain : a journal of neurology* 2008; **131**(Pt 12): 3239-45.
9. Fisher RS. The New Classification of Seizures by the International League Against Epilepsy 2017. *Current neurology and neuroscience reports* 2017; **17**(6): 48.
10. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017; **58**(4): 512-21.
11. Tomson T, Nashef L, Ryvlin P. Sudden unexpected death in epilepsy: current knowledge and future directions. *The Lancet Neurology* 2008; **7**(11): 1021-31.
12. Nilsson L, Farahmand BY, Persson PG, Thiblin I, Tomson T. Risk factors for sudden unexpected death in epilepsy: a case control study. *The Lancet* 1999; **353**(9156): 888-93.
13. Hesdorffer DC, Tomson T, Benn E, et al. Do antiepileptic drugs or generalized tonic-clonic seizure frequency increase SUDEP risk? A combined analysis. *Epilepsia* 2012; **53**(2): 249-52.
14. Thurman DJ, Hesdorffer DC, French JA. Sudden unexpected death in epilepsy: assessing the public health burden. *Epilepsia* 2014; **55**(10): 1479-85.
15. Devinsky O, Hesdorffer DC, Thurman DJ, Lhatoo S, Richerson G. Sudden unexpected death in epilepsy: epidemiology, mechanisms, and prevention. *The Lancet Neurology* 2016; **15**(10): 1075-88.
16. Lamberts RJ, Thijs RD, Laffan A, Langan Y, Sander JW. Sudden unexpected death in epilepsy: People with nocturnal seizures may be at highest risk. *Epilepsia* 2011; **53**(2): 253-7.

17. Perucca E, Beghi E, Dulac O, Shorvon S, Tomson T. Assessing risk to benefit ratio in antiepileptic drug therapy. *Epilepsy Res* 2000; **41**(2): 107-39.
18. Marson A, Jacoby A, Johnson A, Kim L, Gamble C, Chadwick D. Immediate versus deferred antiepileptic drug treatment for early epilepsy and single seizures: a randomised controlled trial. *Lancet (London, England)* 2005; **365**(9476): 2007-13.
19. Luoni C, Bisulli F, Canevini MP, et al. Determinants of health-related quality of life in pharmacoresistant epilepsy: results from a large multicenter study of consecutively enrolled patients using validated quantitative assessments. *Epilepsia* 2011; **52**(12): 2181-91.
20. Gilliam F, Carter J, Vahle V. Tolerability of antiseizure medications: implications for health outcomes. *Neurology* 2004; **63**(10 Suppl 4): S9-s12.
21. Perucca P, Gilliam FG. Adverse effects of antiepileptic drugs. *The Lancet Neurology* 2012; **11**(9): 792-802.
22. Baker GA, Jacoby A, Buck D, Stalgis C, Monnet D. Quality of life of people with epilepsy: a European study. *Epilepsia* 1997; **38**(3): 353-62.
23. McCorry D, Chadwick D, Marson A. Current drug treatment of epilepsy in adults. *The Lancet Neurology* 2004; **3**(12): 729-35.
24. Malmgren K, Reuber M, Appleton R. Oxford Textbook of Epilepsy and Epileptic Seizures. In: Shorvon S, Guerrini R, Cook M, Lhatoo S, eds. *Differential Diagnosis of Epilepsy*: Oxford University Press; 2012: 81-94.
25. Blum ED, Eskola JJ, Bortz SJ, Fisher SR. Patient awareness of seizures. *Neurology* 1996; **47**(1): 260-4.
26. Hoppe C, Poepel A, Elger CE. Epilepsy: accuracy of patient seizure counts. *Archives of neurology* 2007; **64**(11): 1595-9.
27. Inoue Y, Mihara T. Awareness and responsiveness during partial seizures. *Epilepsia* 1998; **39 Suppl 5**: 7-10.
28. Kerling F, Mueller S, Pauli E, Stefan H. When do patients forget their seizures? An electroclinical study. *Epilepsy Behav* 2006; **9**(2): 281-5.
29. DuBois JM, Boylan LS, Shiyko M, Barr WB, Devinsky O. Seizure prediction and recall. *Epilepsy Behav* 2010; **18**(1-2): 106-9.
30. Fisher RS, Blum DE, DiVentura B, et al. Seizure diaries for clinical research and practice: limitations and future prospects. *Epilepsy Behav* 2012; **24**(3): 304-10.
31. Elger CE, Hoppe C. Diagnostic challenges in epilepsy: seizure under-reporting and seizure detection. *The Lancet Neurology* 2018; **17**(3): 279-88.
32. Jory C, Shankar R, Coker D, McLean B, Hanna J, Newman C. Safe and sound? A systematic literature review of seizure detection methods for personal use. *Seizure* 2016; **36**: 4-15.
33. Bidwell J, Khuwatsamrit T, Askew B, Ehrenberg JA, Helmers S. Seizure reporting technologies for epilepsy treatment: A review of clinical information needs and supporting technologies. *Seizure* 2015; **32**: 109-17.
34. S. LFS. Multimodal seizure detection: A review. *Epilepsia* 2018; **59**(S1): 42-7.

- 35.Lokk J, Borg S, Svensson J, Persson U, Ljunggren G. Drug and treatment costs in Parkinson's disease patients in Sweden. *Acta Neurol Scand* 2012; **125**(2): 142-7.
- 36.Dorsey ER, Constantinescu R, Thompson JP, et al. Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030. *Neurology* 2007; **68**(5): 384-6.
- 37.Driver JA, Logroschino G, Gaziano JM, Kurth T. Incidence and remaining lifetime risk of Parkinson disease in advanced age. *Neurology* 2009; **72**(5): 432-8.
- 38.Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Movement disorders : official journal of the Movement Disorder Society* 2014; **29**(13): 1583-90.
- 39.de Lau LML, Breteler MMB. Epidemiology of Parkinson's disease. *The Lancet Neurology* 2006; **5**(6): 525-35.
- 40.Kalia LV, Lang AE. Parkinson's disease. *The Lancet* 2015; **386**(9996): 896-912.
- 41.Chaudhuri KR, Healy DG, Schapira AHV. Non-motor symptoms of Parkinson's disease: diagnosis and management. *The Lancet Neurology* 2006; **5**(3): 235-45.
- 42.Schapira AHV, Chaudhuri KR, Jenner P. Non-motor features of Parkinson disease. *Nature reviews Neuroscience* 2017; **18**(7): 435-50.
- 43.Chaudhuri KR, Prieto-Jurcynska C, Naidu Y, et al. The nondeclaration of nonmotor symptoms of Parkinson's disease to health care professionals: An international study using the nonmotor symptoms questionnaire. *Movement Disorders* 2010; **25**(6): 704-9.
- 44.Martinez-Martin P, Rodriguez-Blazquez C, Kurtis MM, Chaudhuri KR. The impact of non-motor symptoms on health-related quality of life of patients with Parkinson's disease. *Mov Disord* 2011; **26**(3): 399-406.
- 45.Nutt JG, Holford NH. The response to levodopa in Parkinson's disease: imposing pharmacological law and order. *Ann Neurol* 1996; **39**(5): 561-73.
- 46.Mouradian MM, Heuser IJ, Baronti F, Fabbrini G, Juncos JL, Chase TN. Pathogenesis of dyskinesias in Parkinson's disease. *Ann Neurol* 1989; **25**(5): 523-6.
- 47.Olanow CW, Watts RL, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease (2001). *Treatment Guidelines* 2001; **56**(suppl 5): S1-S88.
- 48.Lewitt PA. Levodopa for the treatment of Parkinson's disease. *The New England journal of medicine* 2008; **359**(23): 2468-76.
- 49.Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. *Mov Disord* 2001; **16**(3): 448-58.
- 50.Gray R, Ives N, Rick C, et al. Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial. *Lancet (London, England)* 2014; **384**(9949): 1196-205.

51. Cedarbaum JM. Clinical pharmacokinetics of anti-parkinsonian drugs. *Clinical pharmacokinetics* 1987; **13**(3): 141-78.
52. Lyons KE. Levodopa-related wearing-off in Parkinson's disease: identification and management AU - Pahwa, Rajesh. *Current Medical Research and Opinion* 2009; **25**(4): 841-9.
53. Dewey RB. Management of motor complications in Parkinson's disease. *Neurology* 2004; **62**(6 suppl 4): S3-S7.
54. Nyholm D, Lewander T, Gomes-Trolin C, et al. Pharmacokinetics of levodopa/carbidopa microtablets versus levodopa/benserazide and levodopa/carbidopa in healthy volunteers. *Clin Neuropharmacol* 2012; **35**(3): 111-7.
55. Chaudhuri KR, Martinez-Martin P, Schapira AH, et al. International multicenter pilot study of the first comprehensive self-completed nonmotor symptoms questionnaire for Parkinson's disease: the NMSQuest study. *Mov Disord* 2006; **21**(7): 916-23.
56. Chaudhuri KR, Yates L, Martinez-Martin P. The non-motor symptom complex of Parkinson's disease: A comprehensive assessment is essential. *Current neurology and neuroscience reports* 2005; **5**(4): 275-83.
57. Defer GL, Widner H, Marie RM, Remy P, Levivier M. Core assessment program for surgical interventional therapies in Parkinson's disease (CAPSIT-PD). *Mov Disord* 1999; **14**(4): 572-84.
58. Stacy M, Bowron A, Guttman M, et al. Identification of motor and nonmotor wearing-off in Parkinson's disease: comparison of a patient questionnaire versus a clinician assessment. *Mov Disord* 2005; **20**(6): 726-33.
59. Poochikian-Sarkissian S, Tai P, del Campo M, et al. Patient awareness of seizures as documented in the epilepsy monitoring unit. *Canadian journal of neuroscience nursing* 2009; **31**(4): 22-3.
60. Detyniecki K, Blumenfeld H. Consciousness of seizures and consciousness during seizures: are they related? *Epilepsy Behav* 2014; **30**: 6-9.
61. Blachut B, Hoppe C, Surges R, Stahl J, Elger CE, Helmstaedter C. Counting seizures: The primary outcome measure in epileptology from the patients' perspective. *Seizure* 2015; **29**: 97-103.
62. Papapetropoulos SS. Patient diaries as a clinical endpoint in Parkinson's disease clinical trials. *CNS Neurosci Ther* 2012; **18**(5): 380-7.
63. Arthur A. Stone. SS, Joseph E. Schwartz, Joan E. Broderick, Michael R. Hufford. Patient compliance with paper and electronic diaries. Controlled Clinical Trials. *Controlled Clinical Trials* 2003; **24**(2): 182-99.
64. van Andel J, Thijs RD, de Weerd A, Arends J, Leijten F. Non-EEG based ambulatory seizure detection designed for home use: What is available and how will it influence epilepsy care? *Epilepsy & Behavior* 2016; **57**: 82-9.
65. Schulze-Bonhage A, Sales F, Wagner K, et al. Views of patients with epilepsy on seizure prediction devices. *Epilepsy Behav* 2010; **18**(4): 388-96.
66. Henriksen M, Lund H, Moe-Nilssen R, Bliddal H, Danneskiold-Samsøe B. Test-retest reliability of trunk accelerometric gait analysis. *Gait Posture* 2004; **19**(3): 288-97.

- 67.Hansen BH, Kolle E, Dyrstad SM, Holme I, Anderssen SA. Accelerometer-determined physical activity in adults and older people. *Medicine and science in sports and exercise* 2012; **44**(2): 266-72.
- 68.Greene BR, O'Donovan A, Romero-Ortuno R, Cogan L, Scanail CN, Kenny RA. Quantitative falls risk assessment using the timed up and go test. *IEEE Trans Biomed Eng* 2010; **57**(12): 2918-26.
- 69.Zakaria NA, Kuwae Y, Tamura T, Minato K, Kanaya S. Quantitative analysis of fall risk using TUG test. *Comput Methods Biomech Biomed Engin* 2015; **18**(4): 426-37.
- 70.Montoye HJ, Washburn R, Servais S, Ertl A, Webster JG, Nagle FJ. Estimation of energy expenditure by a portable accelerometer. *Medicine and science in sports and exercise* 1983; **15**(5): 403-7.
- 71.Nijssen TM, Arends JB, Griep PA, Chuitmans PJ. The potential value of three-dimensional accelerometry for detection of motor seizures in severe epilepsy. *Epilepsy Behav* 2005; **7**(1): 74-84.
- 72.Van de Vel A, Cuppens K, Bonroy B, et al. Long-term home monitoring of hypermotor seizures by patient-worn accelerometers. *Epilepsy & behavior : E&B* 2013; **26**(1): 118-25.
- 73.Bayly J, Carino J, Petrovski S, et al. Time-frequency mapping of the rhythmic limb movements distinguishes convulsive epileptic from psychogenic nonepileptic seizures. *Epilepsia* 2013; **54**(8): 1402-8.
- 74.Gubbi J, Kusmakar S, Rao A, Yan B, O'Brien T, Palaniswami M. Automatic Detection and Classification of Convulsive Psychogenic Non-epileptic Seizures Using a Wearable Device. *IEEE J Biomed Health Inform* 2015.
- 75.Velez M, Fisher RS, Bartlett V, Le S. Tracking generalized tonic-clonic seizures with a wrist accelerometer linked to an online database. *Seizure* 2016; **39**: 13-8.
- 76.Lockman J, Fisher RS, Olson DM. Detection of seizure-like movements using a wrist accelerometer. *Epilepsy Behav* 2011; **20**(4): 638-41.
- 77.Van de Vel A, Verhaert K, Ceulemans B. Critical evaluation of four different seizure detection systems tested on one patient with focal and generalized tonic and clonic seizures. *Epilepsy Behav* 2014; **37**: 91-4.
- 78.Beniczyk S, Polster T, Kjaer TW, Hjalgrim H. Detection of generalized tonic-clonic seizures by a wireless wrist accelerometer: a prospective, multicenter study. *Epilepsia* 2013; **54**(4): e58-61.
- 79.Kramer U, Kipervasser S, Shlitner A, Kuzniecky R. A novel portable seizure detection alarm system: preliminary results. *J Clin Neurophysiol* 2011; **28**(1): 36-8.
- 80.Conradsen I, Beniczky S, Wolf P, Henriksen J, Sams T, Sorensen HB. Seizure onset detection based on a Uni- or multi-modal intelligent seizure acquisition (UISA/MISA) system. *Conf Proc IEEE Eng Med Biol Soc* 2010; **2010**: 3269-72.
- 81.Milosevic M, Van de Vel A, Bonroy B, et al. Automated Detection of Tonic-Clonic Seizures Using 3-D Accelerometry and Surface Electromyography in Pediatric Patients. *IEEE J Biomed Health Inform* 2016; **20**(5): 1333-41.

82. Beniczky S, Conradsen I, Henning O, Fabricius M, Wolf P. Automated real-time detection of tonic-clonic seizures using a wearable EMG device. *Neurology* 2018; **90**(5): e428-e34.
83. Halford JJ, Sperling MR, Nair DR, et al. Detection of generalized tonic-clonic seizures using surface electromyographic monitoring. *Epilepsia* 2017; **58**(11): 1861-9.
84. van Andel J, Ungureanu C, Arends J, et al. Multimodal, automated detection of nocturnal motor seizures at home: Is a reliable seizure detector feasible? *Epilepsia Open* 2017; **2**(4): 424-31.
85. Poh MZ, Loddenkemper T, Reinsberger C, et al. Convulsive seizure detection using a wrist-worn electrodermal activity and accelerometry biosensor. *Epilepsia* 2012; **53**(5): e93-7.
86. Onorati F, Regalia G, Caborni C, et al. Multicenter clinical assessment of improved wearable multimodal convulsive seizure detectors. *Epilepsia* 2017; **58**(11): 1870-9.
87. Arends J, Thijs RD, Gutter T, et al. Multimodal nocturnal seizure detection in a residential care setting: A long-term prospective trial. *Neurology* 2018; **91**(21): e2010-e9.
88. Leijten FSS. Multimodal seizure detection: A review. *Epilepsia* 2018; **59**(S1): 42-7.
89. Beniczky S, Ryvlin P. Standards for testing and clinical validation of seizure detection devices. *Epilepsia* 2018; **59**(S1): 9-13.
90. Odin P, Chaudhuri KR, Volkmann J, et al. Viewpoint and practical recommendations from a movement disorder specialist panel on objective measurement in the clinical management of Parkinson's disease. *NPJ Parkinson's disease* 2018; **4**: 14-.
91. Maetzler W, Klucken J, Home M. A clinical view on the development of technology-based tools in managing Parkinson's disease. *Mov Disord* 2016; **31**(9): 1263-71.
92. Murphy MA, Bergquist F, Hagström B, et al. An upper body garment with integrated sensors for people with neurological disorders—early development and evaluation. *BMC Biomedical Engineering* 2019; **1**(1): 3.
93. Ritchie J, Lewis J, Lewis PSPJ, Nicholls CMN, Ormston R. Qualitative Research Practice: A Guide for Social Science Students and Researchers: SAGE Publications; 2013.
94. Malterud K. Qualitative research: standards, challenges, and guidelines. *The Lancet* 2001; **358**(9280): 483-8.
95. Ivanoff SD, Hultberg J. Understanding the multiple realities of everyday life: Basic assumptions in focus-group methodology. *Scandinavian Journal of Occupational Therapy* 2009; **13**(2): 125-32.
96. Patton MQ. Qualitative Research. Encyclopedia of Statistics in Behavioral Science; 2005.
97. Krueger RA. Focus Groups: A Practical Guide for Applied Research: SAGE Publications; 2014.
98. Patton MQ. Qualitative research & evaluation methods: integrating theory and practice. Thousand Oaks, California: SAGE Publications, Inc; 2015.

99. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse Educ Today* 2004; **24**(2): 105-12.
100. Griffiths RI, Kotschet K, Arfon S, et al. Automated assessment of bradykinesia and dyskinesia in Parkinson's disease. *J Parkinsons Dis* 2012; **2**(1): 47-55.
101. Horne MK, McGregor S, Bergquist F. An objective fluctuation score for Parkinson's disease. *PLoS One* 2015; **10**(4): e0124522.
102. Nyholm D, Ehrnebo M, Lewander T, et al. Frequent administration of levodopa/carbidopa microtablets vs levodopa/carbidopa/entacapone in healthy volunteers. *Acta Neurol Scand* 2013; **127**(2): 124-32.
103. Senek M, Aquilonius SM, Askmark H, et al. Levodopa/carbidopa microtablets in Parkinson's disease: a study of pharmacokinetics and blinded motor assessment. *Eur J Clin Pharmacol* 2017.
104. Thomas I, Westin J, Alam M, et al. A Treatment-Response Index From Wearable Sensors for Quantifying Parkinson's Disease Motor States. *IEEE J Biomed Health Inform* 2018; **22**(5): 1341-9.
105. Fahn S. Members of the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. *Recent developments in Parkinson's disease* 1987; **2**: 293-304.
106. Martínez-Martín P, Gil-Nagel A, Gracia LM, Gómez JB, Martínez-Sarriés J, Bermejo F. Unified Parkinson's disease rating scale characteristics and structure. *Movement Disorders* 1994; **9**(1): 76-83.
107. Goetz CG, Stebbins GT, Shale HM, et al. Utility of an objective dyskinesia rating scale for Parkinson's disease: inter- and intrarater reliability assessment. *Mov Disord* 1994; **9**(4): 390-4.
108. Nyholm D, Nilsson Remahl AI, Dizdar N, et al. Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease. *Neurology* 2005; **64**(2): 216-23.
109. Goetz CG, Tilley BC, Shaftman SR, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord* 2008; **23**(15): 2129-70.
110. Jenkinson C, Fitzpatrick R, Peto V, Greenhall R, Hyman N. The PDQ-8: Development and validation of a short-form parkinson's disease questionnaire. *Psychology & Health* 1997; **12**(6): 805-14.
111. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011; **20**(10): 1727-36.
112. Fantino B, Moore N. The self-reported Montgomery-Asberg Depression Rating Scale is a useful evaluative tool in Major Depressive Disorder. *BMC Psychiatry* 2009; **9**: 26.
113. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *The British Journal of Psychiatry* 1979; **134**(4): 382-9.
114. Czarnecki M, Gustafsson N. Machine learning for detection of epileptic seizures. 2015.



<http://publications.lib.chalmers.se/records/fulltext/219371/219371.pdf> (accessed February 28 2018).

115. Cohen J. CHAPTER 3 - The Significance of a Product Moment rs. In: Cohen J, ed. *Statistical Power Analysis for the Behavioral Sciences*: Academic Press; 1977: 75-107.
116. Morgan DL, Morgan D. *Focus Groups as Qualitative Research*: SAGE Publications; 1997.
117. Kitzinger J. Qualitative research: introducing focus groups. *Bmj* 1995; **311**(7000): 299-302.
118. Arends J. Movement-based seizure detection. *Epilepsia* 2018.
119. Heldman DA, Giuffrida JP, Chen R, et al. The modified bradykinesia rating scale for Parkinson's disease: reliability and comparison with kinematic measures. *Mov Disord* 2011; **26**(10): 1859-63.
120. Heldman DA, Filipkowski DE, Riley DE, et al. Automated motion sensor quantification of gait and lower extremity bradykinesia. *Conf Proc IEEE Eng Med Biol Soc* 2012; **2012**: 1956-9.
121. Kim JW, Lee JH, Kwon Y, et al. Quantification of bradykinesia during clinical finger taps using a gyrosensor in patients with Parkinson's disease. *Med Biol Eng Comput* 2011; **49**(3): 365-71.
122. Dai H, Lin H, Lueth TC. Quantitative assessment of parkinsonian bradykinesia based on an inertial measurement unit. *Biomed Eng Online* 2015; **14**: 68.
123. Maetzler W, Domingos J, Srulijes K, Ferreira JJ, Bloem BR. Quantitative wearable sensors for objective assessment of Parkinson's disease. *Mov Disord* 2013; **28**(12): 1628-37.
124. Shameer K, Johnson KW, Glicksberg BS, Dudley JT, Sengupta PP. Machine learning in cardiovascular medicine: are we there yet? *Heart (British Cardiac Society)* 2018; **104**(14): 1156-64.
125. Krittanawong C, Zhang H, Wang Z, Aydar M, Kitai T. Artificial Intelligence in Precision Cardiovascular Medicine. *Journal of the American College of Cardiology* 2017; **69**(21): 2657-64.
126. Deo RC. Machine Learning in Medicine. *Circulation* 2015; **132**(20): 1920-30.
127. Bibault J-E, Giraud P, Burgun A. Big Data and machine learning in radiation oncology: State of the art and future prospects. *Cancer Letters* 2016; **382**(1): 110-7.
128. Breiman L. Statistical modeling: The two cultures (with comments and a rejoinder by the author). *Statistical science* 2001; **16**(3): 199-231.
129. Erickson BJ, Korfiatis P, Akkus Z, Kline TL. Machine Learning for Medical Imaging. *RadioGraphics* 2017; **37**(2): 505-15.
130. Kubota KJ, Chen JA, Little MA. Machine learning for large-scale wearable sensor data in Parkinson's disease: Concepts, promises, pitfalls, and futures. *Mov Disord* 2016; **31**(9): 1314-26.
131. Cuppens K, Karsmakers P, Van de Vel A, et al. Accelerometry-based home monitoring for detection of nocturnal hypermotor seizures based on novelty detection. *IEEE J Biomed Health Inform* 2014; **18**(3): 1026-33.

132. Espay AJ, Bonato P, Nahab FB, et al. Technology in Parkinson's disease: Challenges and opportunities. *Mov Disord* 2016; **31**(9): 1272-82.
133. Tovar Quiroga DF, Britton JW, Wirrell EC. Patient and caregiver view on seizure detection devices: A survey study. *Seizure* 2016; **41**: 179-81.
134. Thomas I, Alam M, Nyholm D, Senek M, Westin J. Individual dose-response models for levodopa infusion dose optimization. *Int J Med Inform* 2018; **112**: 137-42.
135. Thomas I, Alam M, Bergquist F, et al. Sensor-based algorithmic dosing suggestions for oral administration of levodopa/carbidopa microtablets for Parkinson's disease: a first experience. *J Neurol* 2019.
136. Wechsler LR. Advantages and limitations of teleneurology. *JAMA Neurol* 2015; **72**(3): 349-54.
137. Dorsey ER, Glidden AM, Holloway MR, Birbeck GL, Schwamm LH. Teleneurology and mobile technologies: the future of neurological care. *Nature Reviews Neurology* 2018; **14**: 285.
138. Leopold NA, Polansky M, Hurka MR. Drug adherence in Parkinson's disease. *Mov Disord* 2004; **19**(5): 513-7.
139. Grosset D, Antonini A, Canesi M, et al. Adherence to antiparkinson medication in a multicenter European study. *Mov Disord* 2009; **24**(6): 826-32.
140. Fisher JM, Hammerla NY, Rochester L, Andras P, Walker RW. Body-Worn Sensors in Parkinson's Disease: Evaluating Their Acceptability to Patients. *Telemed J E Health* 2016; **22**(1): 63-9.
141. Arends JBAM. Movement-based seizure detection. *Epilepsia* 2018; **59**(S1): 30-5.
142. van Elmpt WJ, Nijsen TM, Griep PA, Arends JB. A model of heart rate changes to detect seizures in severe epilepsy. *Seizure* 2006; **15**(6): 366-75.
143. Goldenholz DM, Kuhn A, Austermuehle A, et al. Long-term monitoring of cardiorespiratory patterns in drug-resistant epilepsy. *Epilepsia* 2017; **58**(1): 77-84.
144. Philippe R, Carolina C, Ilona W, Sandor B. Wearable devices for sudden unexpected death in epilepsy prevention. *Epilepsia* 2018; **59**(S1): 61-6.
145. Schatz I, Bannister R, Freeman R, et al. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. *Clinical Autonomic Research* 1996; **6**(2): 125-6.
146. Tsukamoto T, Kitano Y, Kuno S. Blood pressure fluctuation and hypertension in patients with Parkinson's disease. *Brain Behav* 2013; **3**(6): 710-4.
147. Hellman AM, Shah SP, Pawlowski SM, Duda JE, Morley JF. Continuous non-invasive monitoring to detect covert autonomic dysfunction in Parkinson's disease. *Parkinsonism Relat Disord* 2015; **21**(7): 723-8.
148. Allen J. Photoplethysmography and its application in clinical physiological measurement. *Physiol Meas* 2007; **28**(3): R1-39.
149. Wukitsch MW. Pulse oximetry: Historical review and Ohmeda functional analysis. *International journal of clinical monitoring and computing* 1987; **4**(3): 161-6.

150. Lu S, Zhao H, Ju K, et al. Can photoplethysmography variability serve as an alternative approach to obtain heart rate variability information? *Journal of Clinical Monitoring and Computing* 2008; **22**(1): 23-9.
151. Nitzan M, Babchenko A, Khanokh B, Landau D. The variability of the photoplethysmographic signal - A potential method for the evaluation of the autonomic nervous system. *Physiological Measurement* 1998; **19**(1): 93-102.
152. Naschitz JE, Bezobchuk S, Mussafia-Priselac R, et al. Pulse transit time by R-wave-gated infrared photoplethysmography: review of the literature and personal experience. *J Clin Monit Comput* 2004; **18**(5-6): 333-42.
153. Oliver James J, Webb David J. Noninvasive Assessment of Arterial Stiffness and Risk of Atherosclerotic Events. *Arteriosclerosis, Thrombosis, and Vascular Biology* 2003; **23**(4): 554-66.
154. Peter L, Noury N, Cerny M. A review of methods for non-invasive and continuous blood pressure monitoring: Pulse transit time method is promising? *Irbm* 2014; **35**(5): 271-82.
155. Mukkamala R, Hahn JO, Inan OT, et al. Toward Ubiquitous Blood Pressure Monitoring via Pulse Transit Time: Theory and Practice. *IEEE Trans Biomed Eng* 2015; **62**(8): 1879-901.
156. Pitson DJ, Stradling JR. Autonomic markers of arousal during sleep in patients undergoing investigation for obstructive sleep apnoea, their relationship to EEG arousals, respiratory events and subjective sleepiness. *Journal of Sleep Research* 1998; **7**(1): 53-9.
157. Argod J, Pepin JL, Levy P. Differentiating obstructive and central sleep respiratory events through pulse transit time. *Am J Respir Crit Care Med* 1998; **158**(6): 1778-83.
158. Chakrabarti B, Emegbo S, Craig S, Duffy N, O'Reilly J. Pulse transit time changes in subjects exhibiting sleep disordered breathing. *Respiratory Medicine* 2017; **122**: 18-22.