How Does Technology Development Influence the Assessment of Parkinson's Disease? A Systematic Review

by

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ABSTRACT

Parkinson's disease (PD) is a neurological disorder with complicated and disabling motor and non-motor symptoms. The pathology for PD is difficult and expensive. Furthermore, it depends on patient diaries and the neurologist's subjective assessment of clinical scales. Objective, accurate, and continuous patient monitoring have become possible with the advancement in mobile and portable equipment. Consequently, a significant amount of work has been done to explore new cost-effective and subjective assessment methods or PD symptoms. For example, smart technologies, such as wearable sensors and optical motion capturing systems, have been used to analyze the symptoms of a PD patient to assess their disease progression and even to detect signs in their nascent stage for early diagnosis of PD.

This review focuses on the use of modern equipment for PD applications that were developed in the last decade. Four significant fields of research were identified: Assistance to Diagnosis, Prognosis or Monitoring of Symptoms and their Severity, Predicting Response to Treatment, and Assistance to Therapy or Rehabilitation. This study reviews the papers published between January 2008 and December 2018 in the following four databases: Pubmed Central, Science Direct, IEEE Xplore and MDPI. After removing unrelated articles, ones published in languages other than English, duplicate entries and other articles that did not fulfill the selection criteria, 778 papers were manually investigated and included in this review. A general overview of PD applications, devices used and aspects monitored for PD management is provided in this systematic review.

Dedicated to my parents

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INTRODUCTION

Parkinson's disease (PD) is a complex neurodegenerative disorder that affects the overall quality of life (QoL) of the patient and their caregivers. Approximately 60,000 individuals in the United States are diagnosed with PD each year, while more than 10 million people are living with PD worldwide [45, 83]. PD is accompanied by many significant motor signs: tremor, rigidity, bradykinesia, hypokinesia, postural instability, gait difficulties and freezing of gait. While its pathology is usually based on these motor symptoms, many non-motor symptoms are also manifested with this disease. These non-motor symptoms are commonly evident and, at times, even more, disabling than the motor symptoms. Common non-motor signs of the disease are cognitive impairment, reduced ability to smell, dementia, depression and emotional changes. It is a progressive disorder whose symptoms become more noticeable with age. Only an estimated 4% of people with PD are diagnosed before the age of 50 because it is difficult to detect and treat in its nascent stages.

Currently, the pathology of PD is based on the assessment of the motor and non-motor symptoms during a neurological examination, during which a neurologist watches the patient perform some specific task. This process of diagnosis and evaluation of disease progression by visual inspection is sub-optimal as it can be affected by subjectivity of the clinician. Additionally, the neurologist assigns scores to the tasks performed by the patient during the examination, as described by the Unified Parkinsons Disease Rating Scale (UPDRS) [41] or its updated version, the Movement Disorder Society-sponsored revision of the UPDRS (MDS-UPDRS) [53]. Another rating scale, the Hoehn and Yahr scale (HY) [61] assigns an overall score out of 5 to the patient based on their pathological stage. All these clinical scales are subjective and lead to high inter-rater variability among neurologists and

clinics, and thus they are not entirely reliable. Early and accurate diagnosis of PD is of vital importance as it can help in better prognosis and treatment. It can improve the QoL of the patient, while a misdiagnosis can cause a delay in proper treatment. The treatment plan for a PD patient should also be personalized and adhere to the individual needs and predominant symptoms. The clinical assessment of PD also depends on the change in the symptoms noted in the patient's diary. The credibility of such reports are limited by subjectivity and recall bias of the patient [100, 14].

The medication alone can cost $2,500 a year, and corrective surgeries like Deep Brain Stimulation (DBS) cost up to $100,000 per person [45]. For example, imaging equipment, such as magnetic resonance imaging (MRI), single-photon emission computed tomography (SPECT) and positron emission tomography (PET), are used to assist the neurologist in making an objective and more accurate diagnosis [141]. The high cost of such equipment factor into the expenses of diagnosis and treatment of Parkinson's Disease [18]. As a result, many patients tend to ignore their symptoms during the prodromal stage and do not go through proper diagnosis. The primary medication for PD is levodopa, which is highly effective and widely used. However, prolonged usage may lead to complications like Levodopa-Induced Dyskinesia (LID).

Additionally, routine visits to clinics for assessment of disease progression is not ideal for the patients and also not sufficient. Freezing of gait (FoG) and falls are significant causes of injuries for PD patients. Since it is not possible for caregivers to be vigilant and continuously monitor the movements of the patients, an automated monitoring system can be useful. Moreover, a remote monitoring platform can assist clinicians with older patients, have progressing disabilities, and have difficulty making regular trips to the clinic.

1.1 Modern Technologies in Parkinson's Assessment

The development of mobile computing technologies has made the long-term objective measurement of symptoms in PD possible. Popular devices include Inertial Measurement Units (IMUs), Force and Pressure plates, Biopotential sensors, and Optical Motion Capturing Systems. IMUs usually include sensors like accelerometer and gyroscope which can record essential data for analyzing the symptoms of a patient. Force sensors in a force plate can give information about the patient's posture and balance. Neural activity and muscular response can be measured using biopotential sensors like Electroencephalogram (EEG) and Electromyogram (EMG), while Optical Motion Capturing systems like VICON and Microsoft Kinect can be used for body motion analysis of a patient in their ambulatory environment. With the growing popularity of Body Area Network (BAN), Wide Area Network (WAN) and communication protocols like Zigbee and Bluetooth, the networking of these sensors have also become more straightforward. In the last decade, a growing number of scientists have developed innovative assessment techniques for PD using modern technologies. Acceleration data collected during a walking task or a Timed up and Gait examination is recorded for gait quality assessment of a patient. Data collected from IMUs have also been used for identifying physical activities for continuous monitoring [13]. Furthermore, EMG data recorded from the skin of a patient is used to measure tremor. The measurement of these symptoms is then used to determine the severity of the symptoms or to aid in the diagnostic procedure.

1.2 Limitations in Modern Technologies

The use of modern technologies has shown promising results so far. Still, their widespread adoption is limited by many technical and acclimatization challenges [14]. The International Parkinson and Movement Disorders Society Task Force on Technology listed

the problems as limited compatibility between sensors used, discrepancy between clinical needs and scientific research, lack of biomarkers for monitoring non-motor symptoms, relevance of data collected by sensors, lack of efficient algorithms for analyzing sensor data and practical limitations in patients using the technologies for continuous monitoring under a tight energy budget [40, 12]. Majority of the systems developed with modern technologies focus on the motor symptoms of PD, such as, tremor, bradykinesia, gait abnormalities, dyskinesia [40, 117, 141, 104, 36, 35, 118]. Few studies focused on the non-motor symptoms of the disease, such as depression, dementia, cognitive impairment [29, 79, 37, 19, 133]. The measurement of non-motor symptoms is still based on clinical measurements, like blood pressure, and MRI scan. Thus there is an urgent need of developing cost-effective, unobtrusive measurement techniques for non-motor symptoms for remote monitoring of patients.

The lack of a large sample size for testing of solution limits their credibility and generalizability. For a solution to be accepted clinically, it should be tested on a large number of PD patients to ensure that it is not specific to a particular category of symptoms or personalized for a small set of subjects. Finally, the bridge between the clinical needs and scientific research can limit the development of specific technology-based objective measurements (TOMs) [40, 14]. A cohort between the clinical and technical community to develop symptoms-specific TOMs and identify the efficient analysis techniques is required. Figure 1.1(a) illustrates the current assessment of PD symptoms. The health professionals assess the patients during periodic clinic visits, and the technology professionals develop measurement devices for PD assessment. But there is none or little information exchange between the three groups. A better approach is illustrated in Figure 1.1(b) where the technology professionals consult the clinicians to know what is required to be measured and to identify the TOMs. The patients or users give feedback about their experience. These inputs help technology professionals develop a personalized device for objective measure-

ment of PD symptoms. The user and the clinicians also get regular feedback from the device which enables continuous monitoring of symptoms.

Advances in wearable computing system enable a wide range of monitoring, diagnosis, and therapy applications [78, 95, 101]. For example, wearable devices can be used for human activity recognition [72, 13], assistive technologies [94, 93, 138], and decoding human intent [120, 49], The ability to record data from specific sensors is not sufficient unless there is a proper algorithm to analyze the data set and reveal disease-specific information. Clinical expertise is needed to identify reliable features, while technical knowledge is required to develop and use advanced data analysis techniques. Furthermore, adaptation challenges require the technology developers to consider user comfort, in technical requirements [100]. A universal monitoring system should be flexible, inconspicuous, easy to use and easy to manage [14]. Recently proposed wearable devices based on flexible hybrid electronics address these problems by presenting physically wearable devices [15, 55]. Another adaptation challenge is repeated charging requirements, which can be difficult for the user and cause distress [100]. Therefore, there is also a strong need for multi-modal energy harvesting and optimum energy management techniques to improve the usability of wearable devices by eliminating battery charging requirements [16, 103].

1.3 Key Contributions

This thesis presents a systematic review of articles published between January 1, 2008, and December 31, 2018. An electronic database search in Pubmed Central, Science Direct, IEEE Xplore, MDPI was done to retrieve the relevant articles. After the automatic filtering using the keywords, these articles are inspected and classified manually. We identified the following aspects of these papers: (1) The application areas of the proposed solution, (2) the symptoms measured for the application, (3) the devices used for measuring the symptoms, and (4) the sensors included in the devices. The papers under study and our

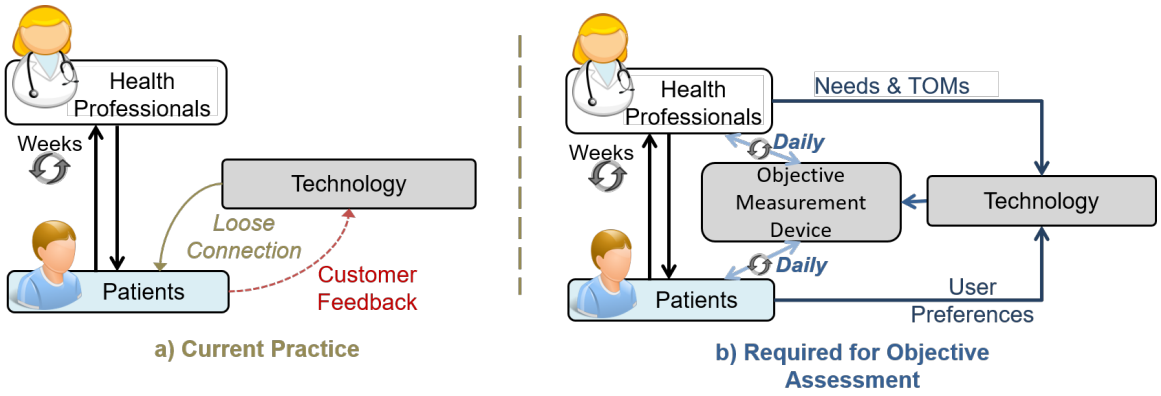

Figure 1.1: (a) Current practice of healthcare for Parkinson's Disease assessment (b) Requirement for objective assessment of Parkinson's Disease

classification are saved in a spreadsheet and released to the public at `https://bit.ly/2HVwKZ0`. The spreadsheet can be updated as new solutions are developed in the future. Hence, it can serve as a platform for technology professionals and clinicians to find innovative developments in the area. Furthermore, this spreadsheet can be used by researchers working in this area to compare their work with the other existing work in their field. The manually labeled data from this spreadsheet can also enable automatic classification of papers studying PD symptoms with modern devices.

We have also developed an automated filtering framework for articles focusing on PD assessment with novel technologies based on their content in Title, Abstract, and Keywords (TAK). The filtering criteria are made following the PRISMA standards, and they follow the PICO strategy [74]. Manual filtering is limited by time and subjectivity, which can be avoided by our filtering framework. It can objectively select the relevant articles for any systematic review or for finding the related literature in a specific field of work. It can also detect duplicate items across multiple databases and filter them out. The automated script makes the review easily reproducible for publications published in the future.

We also use the categorized articles to:

- Analyze the trends in the use of technology for PD research. For example, we use the data to identify the most popular application areas and the areas that receive increasing attention.
- Analyze the devices used in each application area, and how the use of devices has progressed in the last decade.
- Analyze the symptoms measured to develop solutions in each application area and determine the most useful devices for measuring the different traits.
- Examine the overall trend of research in this field and how it is going to progress in the coming years.

1.4 Thesis Organization

The rest of this thesis is organized as follows. In Chapter 2, we discuss the related research which has worked on a systematic review of different articles focusing on new assessment techniques of Parkinson's Disease or its symptoms and analyzed them. In Chapter 3, we start by introducing the search and filtering methodology, then we show that it is performed following the PRISMA guidelines and PICO strategy. Then, we elaborate the classification methodology, where we describe each of the four application areas, the device categories and the symptom areas measured. We also explain the criteria for inclusion in these categories. After this, we explain the analyzing strategies. Chapter 3 also presents the percentage of articles in each application area and the number of articles using each device and symptoms. Chapter 4 describes the results of the classification and the analysis of the results. We analyzed the articles in each application areas and highlighted some of the most notable works in these areas. The classification snapshots of these articles are elaborated in Tables 4.1 - 4.4. We also analyze the different devices used and the notable works related to the devices. The device usage trend and the most commonly used devices

for each application area are also discussed.

Additionally, we discuss the symptoms measured and the devices used for their measurements. We also observe the traits that have not been sufficiently given focus in the last decade. Finally, Chapter 5 presents the outcome as well as the direction for future work.

Chapter 2

RELATED WORK

A large number of studies have been conducted in recent years that investigated the use of wearable sensors and other technologies to assess the symptoms of a patient suffering from neurological disorders [40]. There is also a growing interest in getting an unbiased analysis of the efficacy of technology-based devices that can be used in scientific research of health monitoring and clinical practices [52]. For example, Godinho et al. reviewed 168 articles after searching the PubMed database and grouped the studies based on the type of device used [52]. They classified the devices as (i) 'recommended', (ii) 'suggested' or (iii) 'listed' based on the following criteria: (1) used in the assessment of Parkinson's disease, (2) used in published studies by people other than the developers, and (3) successful clinimetric testing. They concluded that objective sensing technology is gaining a lot of attention in the study of Parkinson's Disease, but the clinimetric properties and testing of the devices remain a controversy. They surmised that PD symptoms like postural control, bradykinesia, tremor, freezing, dyskinesia, gait, and daily activity/physical activity could be objectively measured using the reviewed devices.

With the increased use of smart technologies, their application in the assessment of PD symptoms has also increased in recent years [117]. With the advancement in wearable technologies, early diagnosis, differential diagnosis and objective quantification of symptoms over time have become much easier for clinicians. Wearable sensors have shown promise in PD diagnosis and management, as well as for other pathology [59, 116, 23, 35]. For example, Daneault discussed how wearable and mobile technologies could improve the management of Essential Tremor (ET) [35]. ET is one of the most common movement disorders, and millions of people are affected by it worldwide. Due to several barriers, a

method to clinically manage its symptoms still does not exist. The study proposed 7 different areas in which mobile and wearable technology can improve the clinical management of ET and review the current state of research in these areas. The author concluded that the presence of mobile and wearable technology everywhere could be leveraged to improve the quality of life of the patients if clinicians, engineers, and computer scientists work together on addressing the current knowledge gaps.

The International Parkinson and Movement Disorders Society Task Force on Technology had summarized their deliberations about the growing influence of technology in the diagnosis and monitoring of PD patients in the last 10 years [40]. Espay et al. specifically looked into the Task Force finding on the challenges and opportunities in the development of technologies with the potential for improving the clinical management and QoL of patients with PD. The Task Force stated the importance of identifying technology-based objective measures (TOMs) to improve the sensitivity, accuracy, reproducibility, and feasibility of objectively capturing the full complexity and diversity of changes in motor and non-motor behavior. After reviewing the different advances in using wearable and other new technologies for PD assessment, 6 challenges were identified: (1) the need for monitoring non-motor symptoms, (2) limitations of sensors used to control motor symptoms, (3) discrepancy between clinical needs and research, (4) lack of compatibility among wearable systems, (5) limitations of available analytical methods, and (6) practical limitations in user engagement. The review also identified the new opportunities that wearable systems provide: (1) standard measurement platform, (2) multi-domain measurements, (3) better phenotyping and subtyping, (4) precision medicine, (5) closed-loop (feedback) systems, (6) real-time symptom tracking, (7) the promise of remote monitoring, and (8) better monitoring, better patient engagement, better outcomes. They concluded that, despite all the challenges, the new and upcoming technologies had enabled the collection of disease-relevant data. They further stated that to be able to leverage this opportunity into enhanced

care, better self-management options for PD patients and overall improved healthcare outcomes, technologies need to be: (1) developed as open platforms and integrated with electronic medical record systems, (2) suitable for the acquisition of data that captures motor and non-motor phenomena, and (3) incorporated in treatment delivery systems.

Vienne et al. provided a thorough assessment of features of IMUs and their clinimetric characteristics [137]. In their systematic review, they compared the InertiaLocoGraphy (ILG) protocols, analyzed the features extracted from inertial signals and proposed a semiological analysis of the quality of the measurements. They searched PubMed, Chochrane and EMBASE for articles assessing gait quality by IMUs, published between January 1, 2004, to August 31, 2016. A total number of 78 full-text articles were selected, and the following pathological conditions about the studies were identified from them: (1) Environment: laboratory vs. ambulatory, (2) Floor type and sequence of steps, (3) Walking speed, (4) Sensitization tactics, (5) Aid. Furthermore, they inspected the studies to determine the choice and position of the sensor. In a different study by Rodgers et al., recent advances in wearable sensors and systems that monitor movement, physiology, and environment were discussed [116]. The articles presented in this review were studies focused on applications for PD, stroke, and head and neck injuries. This review examined the advances in "non-invasive sensor" that monitors activities, the environment, and physiologic functions. They analyzed a collection of recent technology advances and applications that show the potential of these technologies to improve the Quality of Life of the patients. Three primary medical use-cases for wearable sensors are described: (1) Parkinson's Disease, (2) Stroke Management, and (3) Head and Neck Injuries. Selected research articles in each of these use cases were discussed. They concluded that recent advances in flexible electronics show great promise for healthcare monitoring. They further stated the importance of developing non-invasive techniques for assessing non-motor symptoms like mental state, attention span and other physiological metrics with high accuracy.

In recent years, a significant amount of research effort has concentrated on analyzing gait quality using wearable sensors. However, there is still little consensus among the research community regarding the efficacy of these studies in detecting gait disturbances like Freezing of Gait (FoG) and falls. De Lima et al. presented an overview of the use of wearable devices to detect FoG and falls in PD and assess their performance [36]. They conducted a systematic search in the PubMed and Web of Science databases using a group of concept keywords. A total of 27 articles were selected, of which 23 were related to FoG and 4 to falls. Data extraction was performed using a predefined table. Extracted variables included: author, sample size, device usage(the type of sensor, number of sensor and sensor location), data collection procedure, and validation results. Validation was defined by the ability of the system to measure a concept that it is supposed to measure. Despite promising validations, the small size of the study samples, the fact that most participants were at the early stage of the disease and that most of the studies were laboratory-based ensured that there was still little consensus of algorithm analysis. They concluded that further work was required in ecological validation and that there was a lack of consistency in the validity measures and the results reported.

Disease management and development of new treatment strategies primarily depend on the clinical information derived from rating scales (i.e., UPDRS, H&Y) and patients' diaries. These sources have various limitations concerning validity, inter-rater variability, and continuous monitoring [141]. Low compliance and recall bias [100] also limits the usefulness of patient diaries. Thus, an objective long-term measurement of the motor functions in PD patients is necessary. In a review made by Yang et al., they discussed the recent developments in sensor technology and how those can be possible replacements of the current rating scales [141]. They introduced the objective measurements of motor functions in PD based on the wearable sensors from the perspective of three primary applications: Diagnosis/Early Diagnosis, Home-based monitoring and Severity evaluation/progression

monitoring. This motivated us to create classification criteria based on PD-focused applications. Rovini et al. [117] conducted a systematic review focused on wearable devices for PD applications and identified 5 main fields of work: early diagnosis, tremor, body motion analysis, motor fluctuations, and home and long-term monitoring. The research was conducted using 3 databases: IEEE Xplore, Science Direct and PubMed Central, between January 2006 and December 2016. After applying the selection strategy and exclusion criteria, 136 papers were thoroughly evaluated and included in the review, giving an extensive overview of wearable devices for the management of the different areas of focus in PD management.

Chapter 3

METHODOLOGY

In this chapter, we first present our search methodology for articles from PubMed Central, Science Direct, IEEE Xplore, and MDPI databases. Then, we elaborate on our selection strategy and the exclusion criteria. Subsequently, we explain our procedure for creating the Systematic Spreadsheet and how it can be used to assess PD research trends and influence of various technologies.

3.1 Search Methodology

An electronic database search of articles published between January 1, 2008, and December 31, 2018, was performed in the PubMed Central, Science Direct, IEEE Xplore and MDPI databases. These were chosen to allow both medical and engineering journals to be included in the search process [36]. The systematic search was performed by following the PRISMA guidelines [74]. The search query included just the keyword ”Parkinson” to keep the search broad. The title/abstract/keyword and year filters were used to provide more specificity. The search queries and the number of hits in each database are shown in Table 3.1.

Only original articles published in English between January 2008 and December 2018, related to Parkinson’s Disease are included in this systematic review. A total of 28,140 articles were selected to begin with, of which 11,318 were from PubMed Central, 14,540 were from Science Direct, 1709 were from IEEE Xplore, and 573 articles were from MDPI. After removing articles that were not written in English or were review articles themselves, 22,698 articles were left. The Title, Authors, Publication Title, Year of Publication (YOP), Keywords, Abstract, Keyword, and DOI were accumulated for all of the 22,698 entries.

The methodologies used for downloading the data from the four online databases are also different. The documents were exported in comma-separated values (CSV) format from IEEE Xplore, tab-delimited format from MDPI and BibTex format from Science Direct. While, for PubMed Central, we used a Python-based API, Metapub [91] for an automated search. The information extracted from all of the databases were accumulated and stored together in a .CSV file.

3.2 Filtering Methodology

Information collected from the aforementioned four databases are used as input for an automated filtering script written in Python. Based on the PICO strategy [74], the script uses 4 keyword blocks to implement the selection strategies and the exclusion criteria. The first keyword block had 10 keywords related to the disease (i.e., *"Parkinson", "Parkinson's Disease", "Bradykinesia", "Dyskinesia", "Levodopa", "Freezing of Gait"*). The second block was made of 7 keywords to exclude non-human studies from the study (i.e., *"Rats", "Primates", "Marmoset", "Monkeys", "Mice", "Mouse", "Animal"*). The third keyword block had 66 technology terms related to Parkinson's Disease assessment (i.e., *"Acceleration", "Accelerometer", "Gyroscope", "Magnetometer", "Gyro", "Acc", "Exoskeleton device", "Inertial sensor", "Video recording", "Video camera", "Camera",*

Table 3.1: Search queries used for each database

Database	**Query**	**Years**	**Hits**
Pubmed Central	parkinson[Body - Key Terms] OR parkinson[Abstract] OR parkinson[Title]	2008 - 2018	11318
Science Direct	"parkinson" in Abstract OR Keyword OR Title	2008 - 2018	14540
IEEE Xplore	"parkinson" in Abstract OR Keyword OR Title	2008 - 2018	1709
MDPI	"parkinson" in Abstract OR Keyword OR Title	2008 - 2018	573

"EHealth", "Technology", "Remote monitoring", "Home monitoring", "Telemedicine", "Mobile phone", "Mobile application", "Precision medicine", "Digital health", "Inertial Measurement Unit", "IMU", "Wearable", "Magneto inertial sensor", "Sensor", "Force plate", "Force sensor", "Pressure sensor", "Gait mat", "Smartphone", "Augmented reality", "Kinect", "VICON", "ECG", "EEG", "EMG", "EOG", "MEG", "Electrocardiography", "Electroencephalography", "Electromyography", "Electrooculography", "Magnetoencephalography", "Machine learning", "Classification", "Auditory cue", "Auditory cueing", "Visual cue", "Ha[tic cue", "Vibration", "Gait classification", "Insole sensors", "Leap motion", "Computer vision", "Supervised learning", "Neural networks", "Speech disorder", "Music therapy", "Smart application", "Smartphone application", "Smart watch", "Smart pen", "Touchscreen", "Digitized tablet", "Fitness band", "Optical motion capturing system"). The last keyword block had 11 technology terms related to Parkinson's Disease treatment, which we have excluded from our review (i.e., *"Positron emission tomography, "Single-photon emission computed tomography, "Magnetic Resonance Imaging, "Deep Brain Stimulation, "Transcranial, "Neuroimaging, "Brain imaging, "fmri, "SPECT, "PET, "MRI*). The keyword blocks were used based on an earlier review [122].

We developed a script in Python to automate the proposed process. The script goes through each article's Title, Abstract, and Keywords (TAK) and compares them with the 4 keyword blocks to objectively determine if the material is relevant to our review or can be excluded, as shown in Figure 3.1. The first keyword block is applied in the very beginning, and if it is determined from the TAK that the article is not related to PD, further evaluations skipped. The second keyword block is then applied to exclude items if the study conducted was on non-human subjects like rats or monkeys. This keyword block also determines the clinical feasibility of the studies. The fourth keyword block is then applied to exclude established diagnostic equipment like Magnetic Resonance Imaging (MRI), Single-photon

emission computed tomography (SPECT), Positron emission tomography (PET) and treatment methodologies like Deep Brain Stimulation (DBS). Excluding this equipment and procedures ensures that the studies reviewed are novel approaches for PD assessment. Finally, the third keyword block is applied to implement the selection strategy. The TAK is compared with the keywords from this keyword block to determine if the article is using any technological approach for solving some problem in Parkinson's Disease.

Our automated filtering process excluded 20,775 articles from the complete list. The second keyword block excluded 831 articles as they involved studies with technologies which are out of the scope of this review. 4170 articles were found to be dealing with non-human subjects by the third keyword block. 15,774 articles were found to be unrelated to the topics of this review. 1923 articles were selected by the script to be fit for our study. We then removed the duplicate entries from the set of selected articles and finally are left with 1830 articles. The filtering keywords applied by the automated script accidentally includes unrelated articles. For example, articles with the terms like "sensor" or "acceleration" are

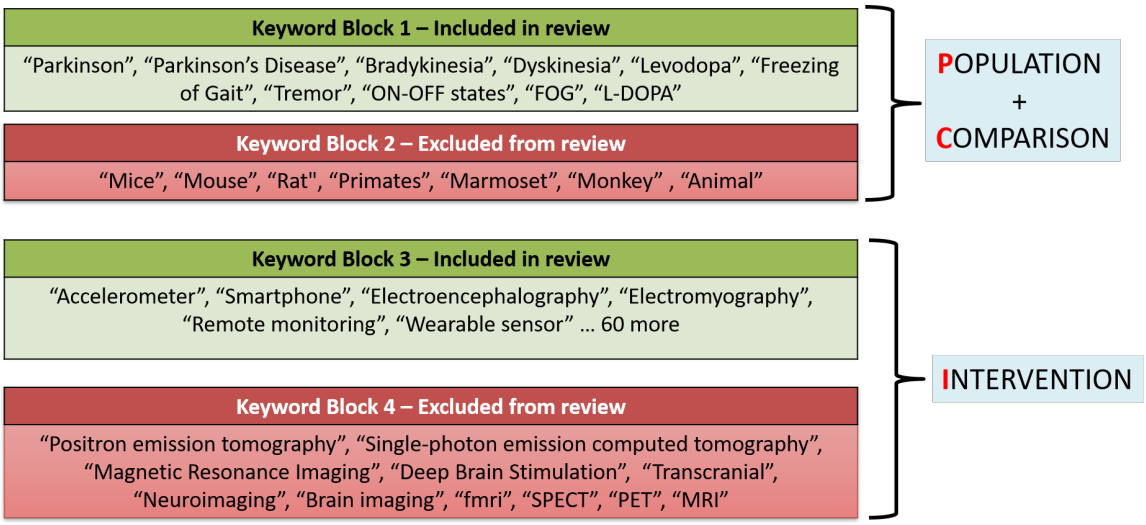

Figure 3.1: Keyword blocks constructed according to PICOS strategy to determine relevance of a paper to this review

included by the script even if they are unrelated; also articles that used “ECG” to monitor “Wolff-Parkinson-White (WPW) syndrome” gets accidentally included by the script. Such articles are excluded manually during the classification of documents. After manual inspection 778 articles were identified as relevant and were classified (Figure 3.2).

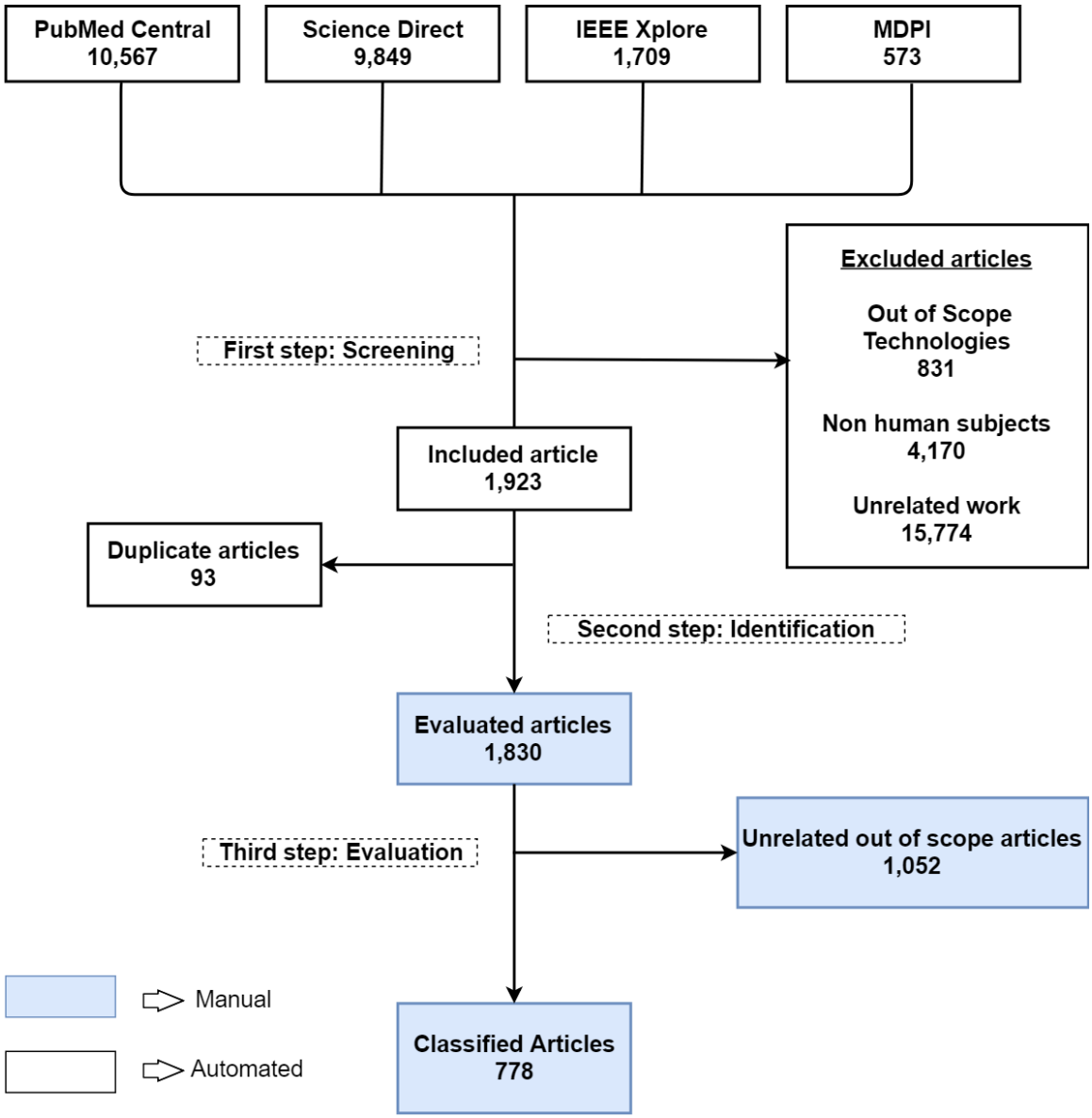

Figure 3.2: Flow diagram of the systematic review process to new technologies used in assessment of Parkinson’s Disease in the last ten years

The articles are saved in a spreadsheet and manually classified using a fixed set of guidelines as described in Section 3.3. The full flow starting from searching the databases to the ultimate collection of articles left for manual analysis is illustrated in Figure 3.2.

The Python code used for filtering and removing the duplicate articles will be made available to the public to offer future studies the opportunity to augment on our review and include more articles to our database.

3.3 Classification Methodology

The 778 articles were analyzed manually to identify the application areas, the devices used and the symptoms monitored as shown in Figure 3.2. The details of all the evaluated papers are listed in the publicly shared table made available at `https://bit.ly/2HVwKZ0`.

3.3.1 Application Areas

We identified four major application area: Diagnosis/Early Diagnosis, Prognosis/Monitoring the severity of Symptoms, Predicting the response to Treatment, and Therapy in general. These were identified based on the earlier reviews [141, 117]. The inclusion criteria for an article to be categorized in either of these classes are as follows:

Diagnosis/Early Diagnosis: To date, the diagnosis of Parkinson's Disease relies on clinical assessment of the motor and non-motor symptoms together, primarily during clinical assessment by neurologists [68]. The neurologist observes the patient perform specific tasks and assigns scores as defined in the Unified Parkinsons Disease Rating Scale (UPDRS) [41] or its updated version, the Movement Disorder Society-sponsored revision of the UPDRS (MDS-UPDRS) [53]. Another popular rating scale is the Hoehn & Yahr scale, which assigns a rating from 1 to 5 to the patient as an overall score of his/her pathologi-

cal progress [61]. The clinical information derived from these rating scales are subjective and leads to inter-rater variability and also intra-rate variability [117, 141]. Currently, the equipment mostly used to supplement the clinicians' assessment is expensive imaging tools like SPECT, PET or MRI. Since the correct diagnosis of PD is essential for prognosis and treatment, objective and cost-effective alternatives to the current tools and techniques are required. Many researchers have been able to use wearable sensors and other devices to differentiate PD patients and healthy controls in lab experiments. Additionally, a significant number of researchers have invested their time in coming up with objective measurements with cost-effective ways to detect early PD patients with minimal motor abnormalities. If an article deals with one of the following problems, we classify it in this category:

- Early Diagnosis of patients with Parkinson's Disease
- Detecting Parkinsonian symptoms in people with untreated PD
- Differentiate patients with Parkinson's Disease from healthy controls or patients with a different neurological disorder
- Differentiate PD-related symptoms from similar symptoms but not caused by PD. For example, differentiating PD tremors from Essential Tremors (ET)

Prognosis/Monitoring the Severity of Symptoms: Currently, the assessment of patient condition and evaluation of PD severity depends primarily on the clinicians' judgment and the patient feedback from diaries and memory. This technique is sub-optimal since it is neither reliable nor objective. The clinicians' judgment is subjective [117, 141] while the patients diary and memory are limited by compliance and recall bias [127, 102, 100]. Thus, objective remote-monitoring of PD symptoms is required to assess disease progression, evaluate the severity of the symptoms and continuously monitor the PD patients in unsupervised environments. If an article deals with one of the following problems, we classify

it as “Diagnosis”:

- Home-based or Remote monitoring of patients with Parkinson’s Disease
- Unsupervised Assisted Living for patients with Parkinson’s Disease
- Evaluating the progression of Parkinson’s Disease in a patient
- Evaluating the severity of PD symptoms in a patient

Predicting Response to Treatment: To measure the efficacy of the treatment or the impact of the medication, clinicians rely mostly on the patients’ complaints and their diaries. These complaints are subjective and unreliable, and they limit the clinicians’ ability to make an effective prognosis to build a future treatment plan. This problem has influenced a lot of research on measuring the impact of a treatment or medication in suppressing the PD symptoms and also to assess their side effects. We look for the following properties in an article to see if it falls in this category:

- Measure the effect of treatment like Deep Brain Stimulation in suppressing the patient’s symptoms over time
- Measure the impact of a medication on the symptoms of the patient
- Measure the side effects of the medicine. For example, levodopa induces dyskinesia

Therapy/Rehabilitation Physiotherapy and other rehabilitation techniques are among the most common treatments for motion disorders like Parkinson’s Disease. Like medication, it is crucial to assess their efficacy. Additionally, it has been observed that cues and feedback are beneficial in assisting a PD patient. A system can provide rhythmic auditory cues, visual cues or haptic cues to facilitate the movement of a patient. Such a system can be used for gait training or to assess limb movements. Vibration-based actuators and audio

feedback are useful to sensitize a patient suffering from Rigidity, Freezing of Gait (FoG), Tremor or other symptoms of PD and help them to break out of the freeze or can even suppress the symptom. Studies that use techniques to assist rehabilitation of a patient are included in this category:

- Audio, Visual or Haptic cue for gait or movement training
- Sensory feedback to suppress a symptom like FoG or Tremor

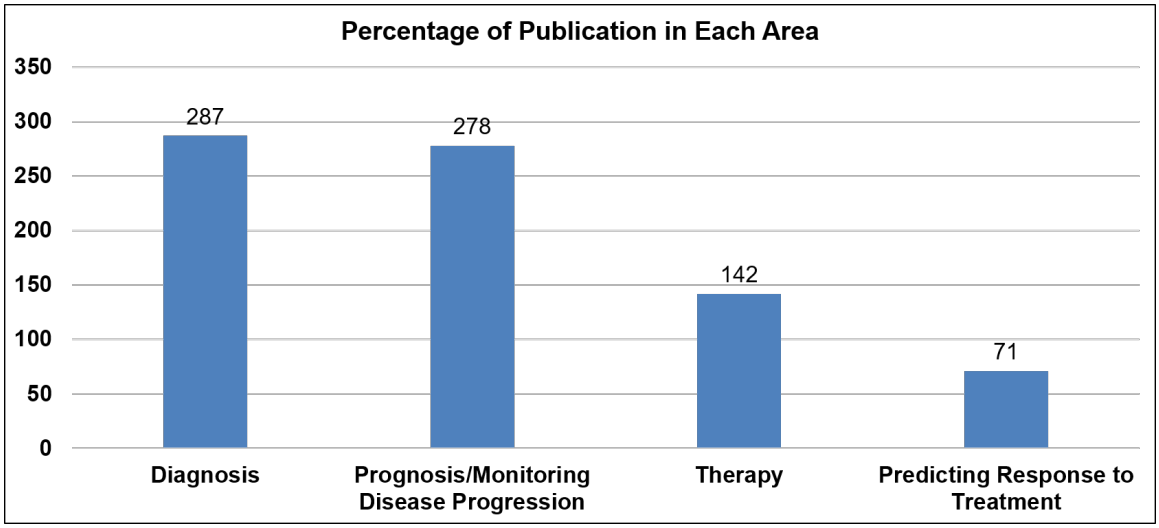

Figure 3.3: Number of publications between 2008-2018 focusing on each application area.

Figure 3.3 shows that the majority of publications have focused on dealing with problems related to Diagnosis and Monitoring of PD patients (i.e., 287 and 278 respectively). A significant share (142) of research papers in this study has also focused on Therapy/Rehabilitation. Using new technologies to predict the impact of medication in PD patients has not been given enough attention yet, as only 71 of the articles in this review focus on this area.

3.3.2 Domain of Research

Symptoms which are used to assess the progression of a PD patient are referred to as cardinal PD features. The cardinal PD features are divided into motor symptoms and non-motor symptoms, as shown in Table 3.2. The motor symptoms are the movement impairments caused due to Parkinson's Disease. These symptoms include cognitive impairment, sleep disturbance, fatigue which do not affect the patient's movement, and these are the non-motor symptoms of PD. Parkinson's Disease also causes impairment of speech, voice and swallowing; such traits are a combination of both motor and non-motor disabilities. Figure 3.4 shows the number of papers that measure the different motor and on-motor symptoms from the documents we have included in this review. Gait abnormalities are the most common symptoms measured, followed by tremor and FoG. Movement disorders like bradykinesia and dyskinesia are also common symptoms in PD patients, and many research articles use modern measurement techniques to monitor these symptoms. The neural response is the most commonly measured non-motor trait for PD assessment.

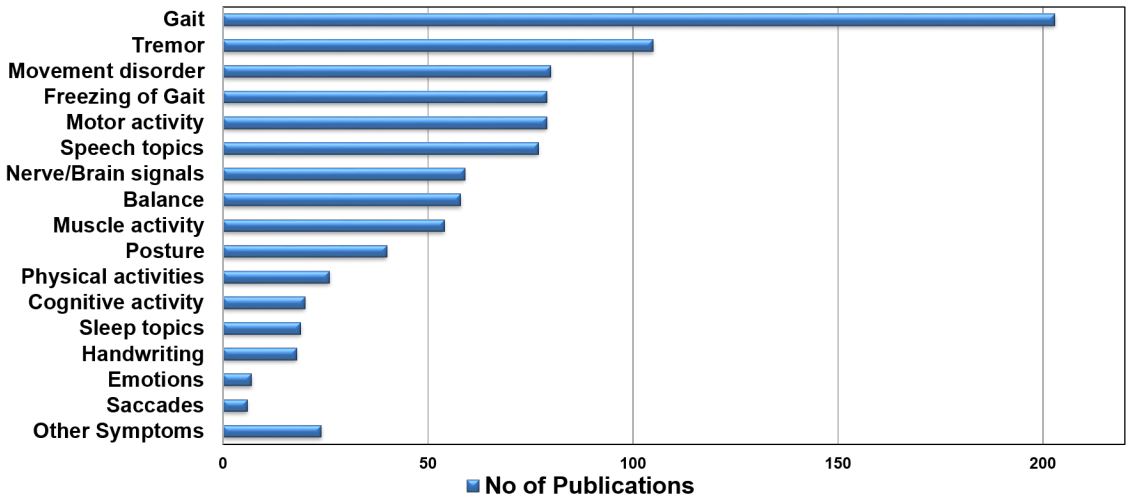

Figure 3.4: Number of publications between 2008-2018 that measure each symptoms.

Table 3.2: Different domains of assessment of Parkinson's Disease using new technologies

Symptoms		
Motor Symptoms	**Non-motor Symptoms**	**Mixed Symptoms**
	Sleep topics	
Gait	Nerve/Brain signals	
Motor activity	Cognitive activity	
Muscle activity	Depression	
FoG	Dementia	
Tremor	Heart rate	Speech topics
Physical activities	Emotions	Swallowing
Movement disorders	Fatigue	
Posture	Facial Expression	
Balance	Blinking	
Nocturnal Hypokinesia	Facial expression	
Handwriting	Breath	
Saccades	Cortical activity	

3.3.3 Overview of the Devices for the Assessment of PD

After analyzing the articles related to applications in Parkinson's Disease, we found that 8 primary types of devices are used as sensors or actuators on PD patients. The devices that form each of the categories and their properties are as follows:

Wearable: Wearable sensors have made recording the symptoms of a PD patient much more comfortable, and many researchers have used wearable sensors in the assessment of a patient. The devices contain sensors such as accelerometer, gyroscope, magnetometer, etc. and when placed in specific parts of the patient's body, parameters such as body movement,

gait speed, stride length, tremor, etc. can be monitored. The following devices are classified as wearables in our study:

1. Inertial Measurement Units using sensors like accelerometer, gyroscope, magnetometer

2. Insole sensors containing force or pressure sensors that can measure the Ground Reaction Force (GRF)

3. Wearable devices that can measure muscle activities or neural responses using EEG, EMG, etc

4. Sensors incorporated with clothes or gloves

5. Other wearable devices like smart glasses or smart caps which can record specific parameters

Biopotential Devices: Devices that can measure the electrical signal (Biopotentials) that are generated by the physiological processes in our body. The tools that fall under this category are Electroencephalogram, Electrocardiogram, Electrocardiogram, Magnetoencephalogram, Electrooculogram, etc.

Cueing Devices: Devices that are used to give feedback or cues to the patients to rectify their walk or to assist with their movement. Headphones or speakers can be used to deliver auditory cues, and visual cues can be provided using a screen or a smart glass or even in a virtual reality environment. Vibration sensors or electrical stimulators have been utilized to give sensory feedback to patients.

Optical Motion Tracker: High-end motion capturing systems, such as Microsoft Kinect and Vicon 3D, are used for motion analysis. A system of multiple IMUs, even camera-based 3D setups are used to capture the movement of a patient.

Audio Recording: Voice and Speech recording devices, such as microphones and smartphones, are used to record the speech tasks or the patient's voice to analyze the speech of the patient.

Video Recording: Patients' movements at home or during laboratory experiments are often recorded using a video camera to spot symptoms or to corroborate with predictions from other devices. Usually, a single video-camera is used to record the patient.

Force/Pressure: During laboratory experiment for gait quality assessment or for analyzing the patients' posture force plates, pressure plates and gait mats that have pressure or force sensors are used.

Smartphone: More researchers are trying to use the sensors present on-board a smartphone (accelerometer, gyroscope, magnetometer, GPS) for different analyses. Smartphone applications are also used to record the patients' mood, emotions and even to record the dosage or medicines. Additionally, the screen of the smartphone can be used to record handwriting, the microphone to record speech samples, and the camera to record patient movements.

Other: There are additional devices apart from the ones already mentioned which have also been used to assess a PD patient. For example, for handwriting assessment, digitized tablets are used as a smart screen to write on during spiralography exams, and smart pens

are used to record hand movement during writing. Virtual Reality and Augmented Reality-based solutions have also started becoming popular in PD applications.

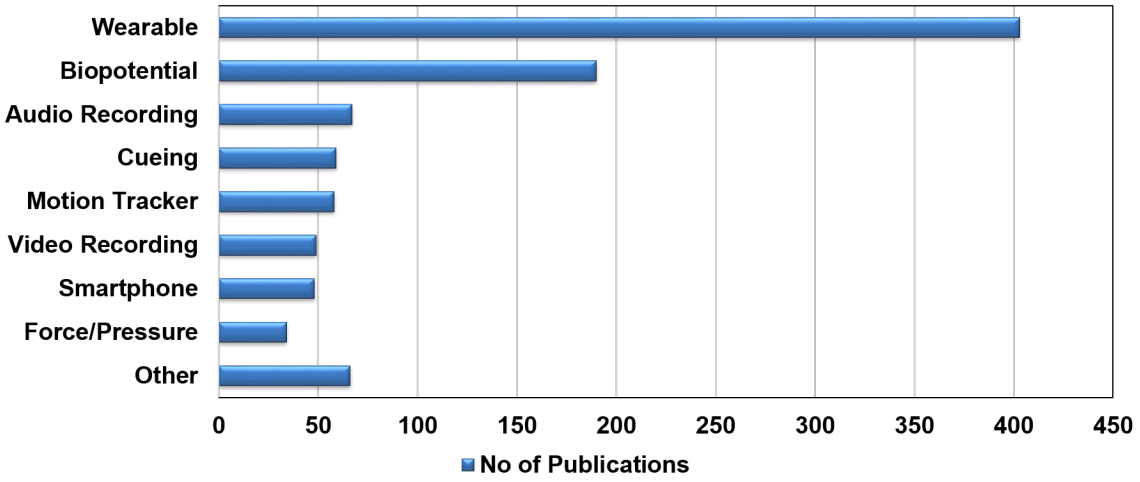

Figure 3.5: Number of publications using new technologies between the years 2008-2018

Figure 3.5 shows that wearable devices are the most commonly used among the papers included in this systematic review. More than 400 articles in this review use some form of a wearable device and close to 200 use a biopotential device. Devices that have features related to more than one categories are included in multiple categories, for example, a wearable device with a biopotential sensor is included in both groups.

3.4 Data Analysis

Following the classification of the articles using the spreadsheet, the trend of research over the last 10 years is analyzed. We find the pattern of the research in this domain according to the application area, the devices used and the field over time. Further study is done to analyze the reason behind the exponential growth in the number of publications and to see if there is any correlation with the use of more mobile technologies.

Chapter 4

RESULTS & ANALYSIS

We observed that of the 778 papers evaluated, 288 (37%) studies focused on diagnosis or assisting in the diagnosis of Parkinson's Disease and 280 (36%) papers are focused on monitoring of patients or prognosis of the disease and the severity of symptoms. Furthermore, 139 (18%) studies were about improving the rehabilitation process of the patients and improving their quality of life, and 70 (9%) studies analyzed the effect of the medication and treatment on the symptoms of the patient as shown in Figure 4.1. A majority of the papers (52%) were published in the last three years (between 2016 - 2018), and 21% papers in just 2018. Figure 4.2 shows the growing interest in finding alternative objective ways of assessing Parkinson's Disease, particularly in the last 3 years.

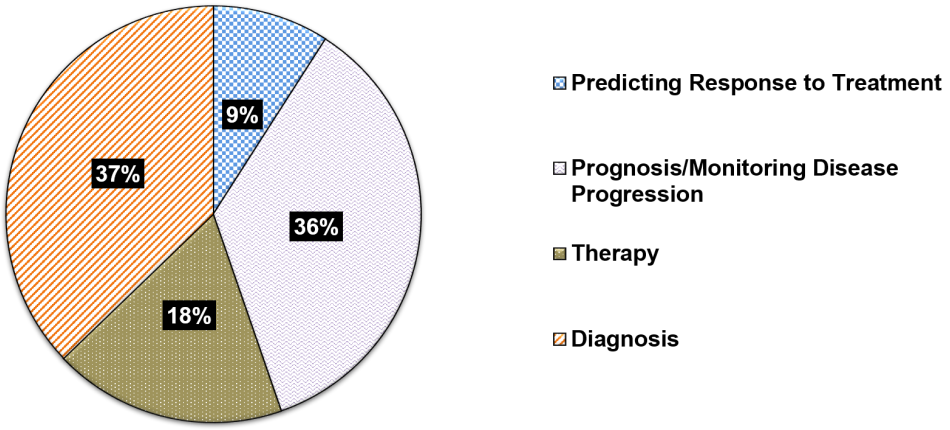

Figure 4.1: Percentage of publications between 2008-2018 by application area

In this section, we analyze the application areas, the symptoms measured in the target studies, and the most commonly used devices. Figure 4.2 shows the of the papers included in our research, the number of articles published every year in the last decade. The total

number of papers published every year has increased at a constant rate. While between the years 2016 and 2018 the growth in the number of articles has been at a higher rate.

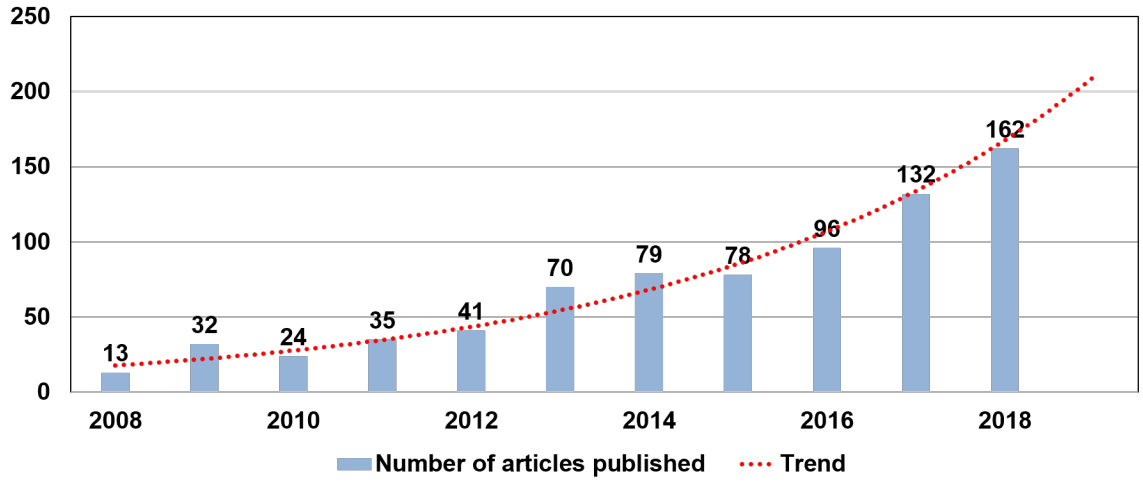

Figure 4.2: Number of publications using new technologies between 2008-2018

4.1 Application Areas

1. Predicting Response to Treatment: Of the papers included in this review, only 9% of articles measured the efficacy of the PD treatment in a patient. Levodopa medication is the most popular treatment for motor and non-motor symptoms of Parkinson's Disease. It helps to alleviate bradykinesia, rigidity, tremors and cognitive dysfunction in people with PD. Still, it is not very clear how such medication improves cognitive or motor operations in patients with Parkinson's Disease. George et al. [48] proposed the theory that dopaminergic drugs improve neural communication by reducing the pathological synchronization within and between the cortex and basal ganglia. They tested their hypothesis by taking scalp EEG of 16 PD patients when ON and OFF medication, once during a resting state and again while performing a stop-signal task. Based on their results, they concluded that dopaminergic medication does improve neural communication during resting state and while performing executive and motor function.

In another study by Herz et al. [60], they analyzed the effect of low and high levels of dopamine on the oscillatory coupling between prefrontal and premotor areas during an externally paced motor task. They recruited 11 patients with PD and 13 healthy controls to perform repetitive extension-flexion movements of their right index finger. EEG data of the participants were recorded while they performed the task. Additionally, the activity in the right first dorsal interosseus (FDI) muscle of the participants was recorded with surface electromyography (EMG). Their results concluded that dopamine deficiency inhibits the ability to establish oscillatory coupling between prefrontal and premotor areas during an externally paced motor task. The effect of levodopa medication in advanced PD was measured using a wireless wearable EMG device by recording signals from biceps brachii and kinematic signals from forearm [119]. In another study, instead of using biopotential sensors, Rigas et al. [111] used a set of wearable sensors to assess PD symptoms and their severity. Based on the analysis of the outputs of the symptoms detection module, the system proposes treatment plans for the patient. Pelicioni et al. used an accelerometer attached to the participant's head using a light plastic helmet liner and another attached mid-back at the level of the sacrum to assess gait stability. The participant's head and trunk stability during gait were examined during, before and after levodopa intake and between individuals who took less than or more than 750mg of levodopa medication each day. The experiment concluded that levodopa intake improved gait stability but only in patients with no postural instability and gait difficulty (PIGD). In patients with PD PIGD, impaired gait stability was not only present but was often worsened by levodopa [105].

Another conventional treatment is Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN). It helps in alleviating motor symptoms and reducing dopaminergic medication. Tabbal et al. used a force transducer to measure rigidity across the elbow, and gyroscope to measure the angular velocity of hand rotation in 52 PD subjects [128]. The participants were tested under 4 DBS conditions: both on, left on, right on and both off.

They quantified the rigidity, bradykinesia and gait speed of the participants. The results showed there was a significant improvement in kinematic inhibitions due to DBS. Also, PD patients with DBS 'OFF' status have larger Lempel-Ziv Complexity (LZC) value compared to when they are in DBS 'ON' state [42]. Wearable sensors were also used to evaluate the efficacy of nocturnal apomorphine infusion in patients suffering from nocturnal hypokinesia [17].

In Figure 4.3, we can observe the trend of research in assessing the efficacy of PD treatment. The interest in this area has grown at a slow rate in the last 10 years and from Figure 4.11 and Figure 4.14, it is observable that wearable and biopotential devices are commonly used devices in this field. The classification criteria for the papers included in this category are described in Table 4.1.

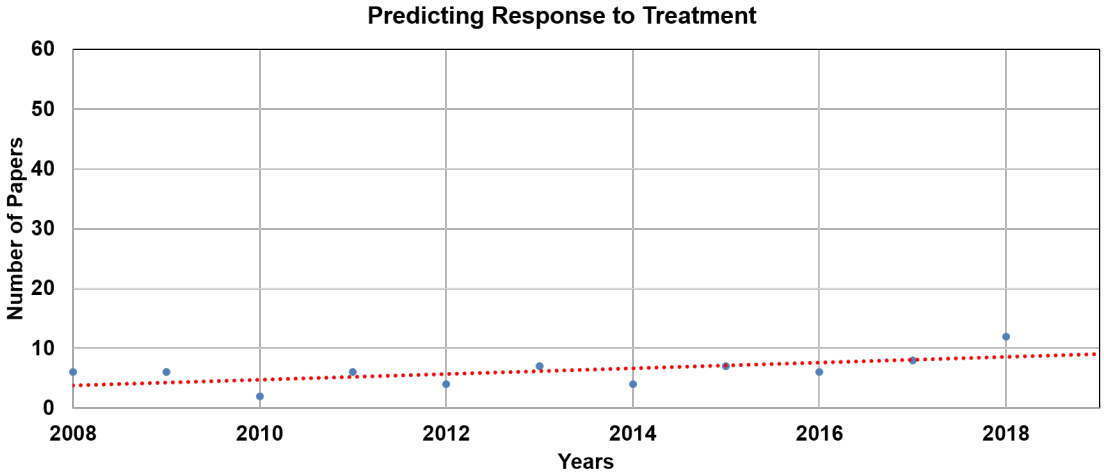

Figure 4.3: Articles published in last 10 years focusing on Predicting Response to Treatment.

Table 4.1: Papers about Predicting Response to Treatment

Reference	Year	Application	Aspect Area	Device	Additional Device	Sensors	No of Subjects (n)
Jobi S. George et al. [48]	2013	Predicting Response to treatment	Movement disorder	Biopotential		EEG	$10 < n \leq 20$
Damian M. Herz et al. [60]	2014	Predicting Response to treatment	Nerve/Brain Signals	Biopotential		EEG	$10 < n \leq 20$
Verneri Ruonala et al. [119]	2018	Predicting Response to treatment	Muscle activity	Wearable	Biopotential	EMG	$10 < n \leq 20$
George Rigas et al. [111]	2010	Predicting Response to treatment	Nerve/Brain Signals	Biopotential		EEG	u/k
Paulo H. S Pelicioni et al. [105]	2018	Predicting Response to treatment	Gait,Posture, Balance	Wearable		Accelerometer	> 30
Samer D. Tabbal et al. [128]	2008	Predicting Response to treatment	Motor activity	Wearable		Force sensor, Gyroscope	> 30
Y. Rakhshani Fatmehsari et al. [42]	2011	Predicting Response to treatment	Gait	Wearable		Gyroscope, Accelerometer	≤ 10
Roongroj Bhidayasiri et al. [17]	2016	Predicting Response to treatment	Nocturnal Hypokinesia	Wearable		Accelerometer, Gyroscope	≤ 10
Verneri Ruonala et al. [119]	2018	Predicting Response to treatment	Muscle activity	Wearable	Biopotential	EMG	
Saara M. Rissanen et al. [114]	2015	Predicting Response to treatment	Muscle activity	Wearable	Biopotential	EMG, Accelerometer	
Wesley JE Teskey et al. [129]	2012	Predicting Response to treatment	Movement disorder	Wearable		Accelerometer, Gyroscope	20<n≤30

Table 4.2: Papers about Therapy/Rehabilitation

Reference	Year	Application	Aspect Area	Device	Additional Device	Sensor/Actuator	No of Subjects
Taylor Chomiak et al. [30]	2017	Therapy	Motor activity	Cueing	Wearable	Audio cue	$10 < n \leq 20$
William R. Young et al. [144]	2016	Therapy	Freezing of Gait	Cueing		Audio cue	$10 < n \leq 20$
E. Jovanov et al. [67]	2009	Therapy	Freezing of Gait	Wearable	Cueing	Audio cue, Accelerometer, Gyroscope	≤ 10
Steven T. Moore et al. [90]	2008	Therapy	Gait,Freezing of Gait	Wearable		Accelerometer	$10 < n \leq 20$
M.E. Jenkins et al. [65]	2009	Therapy	Muscle activity	Biopotential		EMG	> 30
Vishnu Vidya et al. [136]	2017	Therapy	Tremor	Cueing		Vibration cue	u/k
Pieter Ginis et al. [51]	2017	Therapy	Gait	Motion Tracker		Motion capture	≤ 10
Juan Camilo Vasquez-Correa et al. [135]	2018	Therapy	Gait, Speech topics, Handwriting	Wearable	Audio Recording, Other	Touchscreen, Microphone, Accelerometer, Gyroscope	
Syed Haidar Shah et al. [56]	2018	Therapy	Freezing of Gait	Wearable		Accelerometer, Gyroscope	
W Nanhoe-Mahabier et al. [96]	2012	Therapy	Balance	Wearable	Cueing	Gyroscope, Vibration cue	10<n≤20
EEH van Wegen et al. [134]	2018	Therapy	Posture,Balance	Wearable	Cueing	Accelerometer, Vibration cue	
William Omar Contreras Lopez et al. [76]	2014	Therapy	Gait	Wearable	Cueing	Audio cue, Accelerometer	
Filippo Casamassima et al. [27]	2014	Therapy	Gait	Wearable	Smartphone,Cueing	Accelerometer,Gyroscope, Magnetometer,Audio cue	

2. Therapy/Rehabilitation: Developing an efficient rehabilitation plan for a PD patient is very important. Rehabilitation techniques may use assistive cues to help the patients in their daily activities or to improve the activity itself. In the last 10 years, a significant number of research (140) has been done on assisting the rehabilitation techniques. A lot of work has also concentrated on coming up with methods to alleviate motor symptoms like freezing of gait (FoG) and tremor but using auditory, haptic or vibratory cues. The decline in motor and cognitive functionalities in PD patients lead to increased risk of falling and reduced quality of life. In-home music-contingent stepping-in-place (SIP) training program use wearable sensor-based technology platforms to improve step automaticity during Dual-Task. Chomiak et al. conducted a study to test the feasibility and efficacy of such a platform. 4-week research using the sensor system embedded in an iPod Touch was used to calculate step height [30]. The measurements were further used to trigger auditory feedback in real-time through wireless headphones. The study showed that wearable systems could be used effectively for music-contingent SIP training.

Sensory cueing is one of the most common methods used for facilitating stepping in people with PD. Recorded sounds of action relevant tasks are more effective in reducing gait variability in PD patients without freezing of gait (nFoG). In their work, Young et al. studied the efficacy of such auditory cues in PD patients with FoG [144]. They used 4 different auditory cues and asked 19 PD patients (10 nFoG and 9 FoG) to perform a SIP task with each of the prompts. The results showed that with action-specific tasks there was a significant reduction in variation and the potential of using action-specific sensory cues for Parkinson's patients with freezing of gait. Another mobile monitoring system for detection and unfreezing of gait (deFOG) uses a wearable inertial sensor for recognizing FoG episodes with minimum latency and deliver acoustic cues using a wearable headset to unfreeze the gait [67]. Moore et al. recorded the vertical linear acceleration of the left shank using an ankle-mounted sensory array [90]. They defined Freeze Index (FI) as the ratio

between the freeze-band and the locomotor-band of the power analysis of the accelerometer measurements. An FI higher than a chosen threshold was classified as "freeze". Such a mobile monitoring system can provide useful feedback and improve management of FoG in PD. Hand tremor is the most common PD symptom. It prevents patients from performing daily activities, i.e., eating, writing, etc. Vidya et al. in their study have used a coin-type vibration motor on the patients' wrist and a micro-controller for generating random vibration patterns by using Pulse Width Modulation [136]. The induced vibration on the wrist distracts the patient's brain from the biomechanical feedback loop with the hand and reduces the hand tremor.

Spatial-temporal parameters of gait were evaluated by Jenkins et al. using an instrumented carpet, and muscle activation were recorded using surface EMG [65]. Forty subjects were tested while using a facilitatory (ribbed) insole and a conventional (flat) insole while walking 20 feet. The results of the experiments showed that using facilitatory insole improved the single-limb support time significantly. Moreover, the use of facilitatory insole normalized the muscle activation sequence of the tibialis anterior. These changes can lead to an overall improvement in the gait quality and stability of the patients. Ginis et al. used a

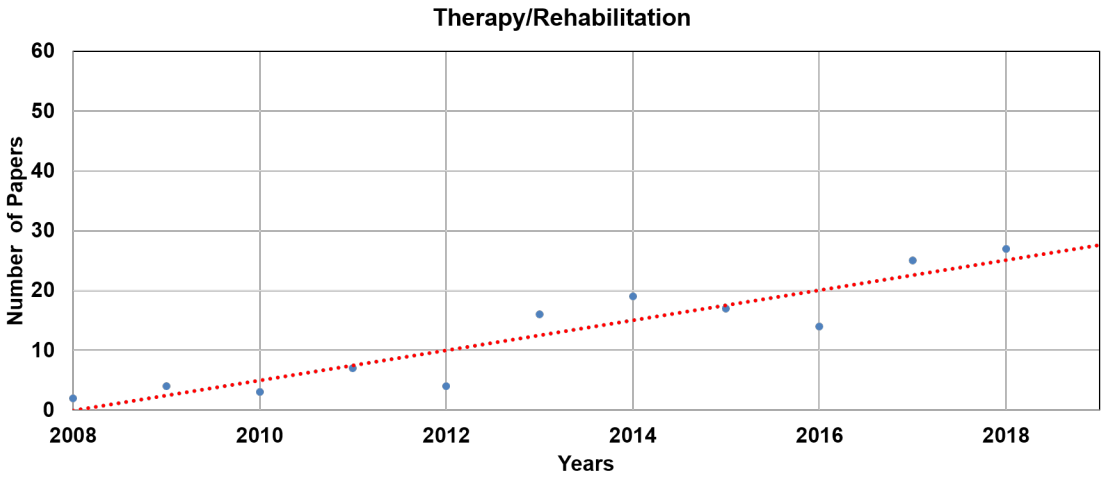

Figure 4.4: Articles published in last 10 years Focusing on Therapy or Rehabilitation of Patients.

motion-capturing system in a 3D camera-based gait laboratory to investigate differences in toe-clearance between people with PD and age-matched healthy elderly [51]. The participants walked for 2 minutes at comfortable pace under 3 conditions: (i) single-task walking, (ii) attending to heel strike during single-task walking, and (iii) dual-task walking. Results showed the people with PD had maximal toe clearance and the attention strategy to focus on heel strike improved the stride length when compared to dual-task walking.

The focus of researchers on improving rehabilitation strategies for people suffering from PD have risen steadily in the last 10 years as shown in Figure 4.5. Table 4.2 describes the classifying approach of papers related to Therapy/Rehabilitation.

3. Prognosis/Monitoring Disease Progression: The assessment of the condition and severity of the symptoms of PD patients depends primarily on the clinician's judgment and the patient's feedback. Since these techniques are sub-optimal and are limited by subjectivity and recall bias, objective home-based monitoring is required. Figure 3.2 shows that between 2008 and 2018, 288 (36%) papers dealt with problems related to tracking of PD patients, assisted living for patients, evaluating the severity of PD symptoms in a patient and evaluating the progression of the disease in general. Zwartjes et al. developed an ambulatory monitoring system that provides a complete motor assessment of a PD patient by simultaneously analyzing motor activities and the severity of several symptoms like tremor, bradykinesia and hypokinesia [149]. The physical movements of 6 PD patients and 7 HCs were measured using a set of 4 inertial sensors and simultaneously video-recorded. The results showed high accuracy in assessing tremor, bradykinesia and hypokinesia, and proved that it could be used to evaluate PD motor symptoms to optimize treatment.

Another study in 2016 suggested the quantification of tremors in Parkinson's patients using smartwatches [32]. This Wireless Body Area Network system is composed of wearable sensor nodes (Android Wear) and one sink node (Android Smartphone). Twelve PD

patients were recruited to perform several activities but were only analyzed during rest. The tremors in the patients were recorded and analyzed in the form of linear acceleration and angular rotation as a function of time. They concluded that this system could be used for determining the evolution of Parkinson's Disease in stage 3 and stage 4 patients. Wan et al. used a smartphone to estimate the severity of Parkinson's Disease in a patient [139]. The study used the UCI data set of voice recording and human activity collected using a smartphone. After extracting features from this data, they ran different classifiers (KNN, Random Forest, Logistic Regression and DMLP). After analyzing the results, they concluded that DMLP performed better than all the other algorithms and that such an approach can improve the precision of treatments and intervention. A recent study proposed the quantification of rest tremors using wearable sensors and a fuzzy inference system [123]. Fifty-seven PD patients underwent a full motor examination on 12 different sessions during which the participants wore a sensor unit on each limb. Fuzzy inference system was applied on the tremor amplitudes measured from the gyroscope data.

In a paper published by Bächlin et al., they developed a wearable assistant to detect FoG events during ambulatory movements [8]. The wearable system uses on-body acceleration sensors to measure patients' movements by analyzing the frequency component of each activity to detect FoG events automatically. Ten PD patients were tested while performing several walking tasks. The system achieved a sensitivity of 73.1% and specificity of 81.6% while detecting FoG. Bayés et al. conducted experiments to analyze the ability of the REMPARK System to detect ON-OFF fluctuations [10]. The system is composed of a sensor and a smartphone. The sensor is worn as a belt near the pelvic region and transmits acceleration data, which are analyzed in real-time by the device microcontroller and transferred to the smartphone via Bluetooth. The algorithms in the device microcontroller use the sensor data to analyze gait, dyskinesia and motor states. After testing the device on 41 patients with moderate to severe idiopathic PD, they concluded that the REMPARK

system can accurately evaluate ON-OFF fluctuations in PD patients.

Timed Up and Go test (TUG) is a commonly used clinical test to evaluate balance and mobility. Salarian et al. proposed an instrumented TUG called iTUG using portable inertial sensors [121]. Twelve patients in early stages of PD were instrumented with inertial sensors and were asked to perform the TUG test. Their recordings from the inertial sensors improved the TUG test in several ways: automatic detection and separation of subcomponents, detailed analysis of each one of them and higher sensitivity than TUG. Robichaud et al. used surface electromyography (sEMG) to evaluate whether changes in EMG pattern during rapid point-to-point movement can be used to distinguish PD patients from healthy controls, and also to determine if the EMG pattern can reflect the severity of PD in the patients [115]. Three groups of 10 PD subjects and 10 HCs performed rapid point-to-point elbow flexion movements. The observations from the experiments showed that the EMG patterns show neurophysiological measures that can objectively distinguish between PD subjects and HCs and also correlate with disease severity.

In another study, Memedi et al. recorded the upper limb movement data of 65 PD patients and 10 HCs as they performed a spiral drawing task on a digitized touch screen telemetry device [87]. The study aimed to characterize motor symptoms like bradykinesia and dyskinesia objectively and to help in automating the visual inspection process of spiral drawing task. The features extracted from the recorded data were fed to a classifier and an accuracy of 84% was achieved in classifying the motor symptoms. Lately, researchers have been focusing on non-motor symptoms like emotions, fatigue, etc. to assess the progression of PD in a patient. For example, Dietz et al. investigated emotional processing in non-demented individuals with PD [38]. Seventeen non-demented PD patients and 16 HCs were shown pleasant, neutral and unpleasant pictures while their electroencephalography (EEG) data were recorded. Late positive potential (LPP) was measured from the EEG data. Apathy, anxiety and depression were assessed in all of the subjects using questionnaire. It

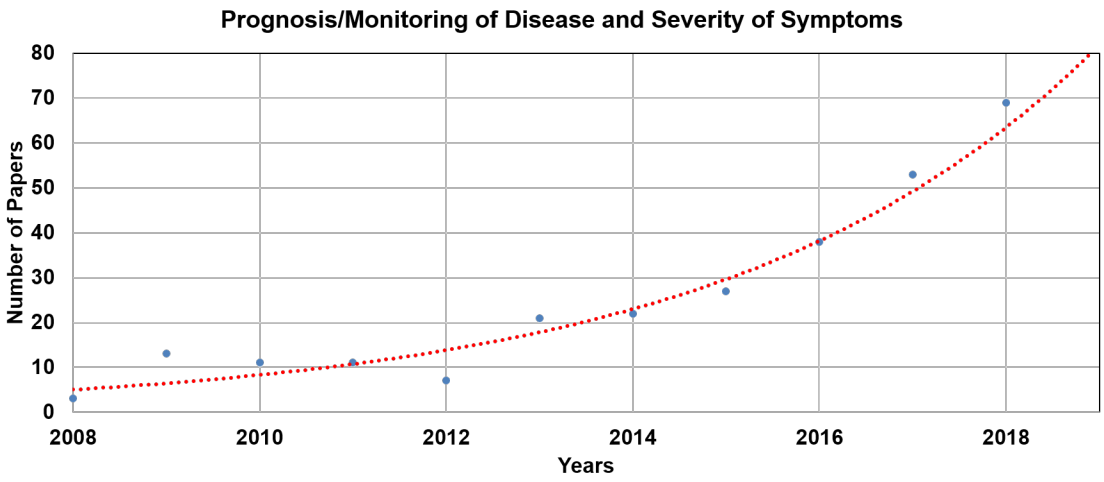

Figure 4.5: Articles published in last 10 years Focusing on Prognosis or Monitoring of Disease and Symptom Severity.

was observed that LPP amplitude during unpleasant picture-viewing was most attenuated for patients reporting high apathy. Other studies like the one conducted by Ricciardi et al. recorded facial expressions of 40 PD patients investigated the relationship between reduced facial expressiveness and altered emotion recognition in PD [110].

The plot in Figure 4.5 shows how the interest of research in this area rose in the last 10 years. Specifically, in the past 3 years, the number of papers published in this area has grown at an exponential rate. Figure 4.11 shows that all modern measuring device has been used in this area, while Figure 4.14 shows that wearable devices are the most used device in these applications. The classification strategy for the articles in this category is illustrated in Table 4.3.

4. Diagnosis: Till date, the diagnosis of PD is dependent on clinical assessment by neurologists using traditional rating scales like UPDRS, MDS-UPDRS or H&Y scale. Expensive imagery equipment like MRI, SPECT and PET are useful to supplement the clinician's assessment. These techniques are prone to inter-rater and inter-clinic subjectivity and can

lead to an incorrect diagnosis. Since a correct diagnosis is of prime importance, several researchers have invested their time in working on improved strategies for diagnosis, which are objective and inexpensive. Raethjen et al. investigated the corticomuscular coherence of Parkinsonian tremor [109] and recorded the scalp EEG data and EMG data from forearm flexors and extensors. This study included tremor data recorded from 21 PD patients and the results showed different cortical representations and corticomuscular interaction of the fundamental and first harmonic frequencies of Parkinsonian tremor. Yoneyama et al. developed an accelerometer-based gait analysis system to differentiate PD patients with gait disorder from healthy controls [143]. They used a single accelerometer attached to the waist of the participants while performing ambulatory activities. A total of 10 PD subjects were included in the study along with 17 age-matched healthy controls. The results of the experiments showed that the average index for PD patients with gait disorder was statistically smaller in value than healthy subjects. Padma G et al. developed a Fiber Bragg Grating Tremor Measurement (FBGTM) device based on a cantilever vibration method to measure hand tremor in PD subjects [131]. The Fiber Brag Grating sensor measured the strain variations created over the cantilever, due to the hand tremor. The frequency analysis of the recorded data can indicate the subject being susceptibility to PD. In recent years, acceleration and EMG measurements were used by Zhang et al. to develop a posture assessment-based system to differentiate between Parkinson's Tremor (PT) and Essential Tremor (ET) [146]. Postural and rest tremor was recorded in 50 subjects, while they underwent 2 experiment sessions of the experiment. The results indicated that arm-rested posture can assist in tremor differentiation.

Muscle activity has been identified as an essential biomarker of early diagnosis of Parkinson's Disease. Annesse et al. implemented a Qualitative Gait Analysis platform for the extraction of muscular response features while performing ordinary activities in PD patients [3]. They proposed a method for quantification of PD symptoms by identifying the

real-time modulation of the muscular index by using 8 EMG wireless nodes positioned on the lower limbs. The platform was examined on 2 PD patients and 2 healthy individuals and the validity of the proposed solution was verified. Another study by Meigal et al. evaluated a variety of novel surface electromyography (sEMG) characteristics of the brachii muscle in patients with PD [86]. Nineteen PD patients, 20 healthy age-matched controls and 20 young controls participated in the clinical experiment where they performed a submaximal isometric holding test. The analyses suggested that the most significant difference between the group of subjects was found in the loading condition when no additional weights were applied in the isometric elbow flexion. They further concluded that sEMG parameters can differentiate between PD subjects from healthy controls and can be used in assessing the severity of PD.

With the rise in use of smartphones, home monitoring and diagnostic aid tools have become possible. Ayena et al. proposed an automatic version of the One-Leg Standing test (OLS) for assessing the risk of falling among older people, using a smartphone [6]. Seven healthy elderly, 4 PD subjects and 12 young adults were recruited for the experiments. The participants completed the OLS test while wearing an instrumented insole to measure the vertical ground reaction force (vGRF) and the smartphone recorded the data. The subjects' center of pressure were assessed from the recorded data and was useful for evaluating the risk of falling. Soubra et al. developed a system using insole sensors to measure the vGRF to identify abnormal gait patterns to detect patients who are potentially affected with PD [126].

EMG data recorded from the chin of a sleeping PD patient to compare the rapid eye movement (REM) sleep chin EMG quantitative features between PD patients with or without REM sleep behavior disorder (RBD) [43]. Twenty-seven PD patients were enrolled in the study and they underwent a full polysomnographic recording. EEG, EMG, and ECG data were recorded and the submentalis muscle EMG was analyzed. The results showed

Table 4.3: Papers about Prognosis or Monitoring of Disease Progression & Severity of Symptoms

Reference	Year	Application	Aspect Area	Device	Additional Device	Sensor/Actuator	No of Subjects
Daphne G. M. Zwartjes et al. [149]	2010	Prognosis/Monitoring Disease Progression	Motor activity,Tremor, Movement disorder	Wearable	Video Recording	Accelerometer,Gyroscope, Video camera	$10 < n \leq 20$
R. Contreras et al. [32]	2016	Prognosis/Monitoring Disease Progression	Tremor	Wearable	Smartphone	Accelerometer,Gyroscope	$10 < n \leq 20$
Shaohua Wan et al. [139]	2018	Prognosis/Monitoring Disease Progression	Speech topics,Physical activities	Smartphone		Accelerometer,Microphone	uk
Luis A. Sanchez-Perez et al. [123]	2018	Prognosis/Monitoring Disease Progression	Tremor	Wearable		Accelerometer,Gyroscope, Magnetometer	> 30
M Bächlin et al. [8]	2010	Prognosis/Monitoring Disease Progression	Gait,Freezing of Gait	Wearable	Cueing	Accelerometer,Audio cue	≤ 10
Àngels Bayés et al. [10]	2018	Prognosis/Monitoring Disease Progression	Movement disorder	Wearable	Smartphone	Accelerometer	u/k
Arash Salarian et al. [51]	2010	Prognosis/Monitoring Disease Progression	Posture,Gait	Wearable		Accelerometer,Gyroscope	$10 < n \leq 20$
JA Robichaud et al. [115]	2009	Prognosis/Monitoring Disease Progression	Muscle activity	Biopotential		EMG	$20 < n \leq 30$
Mevludin Memedi et al. [87]	2015	Prognosis/Monitoring Disease Progression	Handwriting	Other		Touchscreen	> 30
J Dietz et al. [38]	2013	Prognosis/Monitoring Disease Progression	Emotions,Depression	Biopotential		EEG	$10 < n \leq 20$
Lucia Ricciardi et al. [110]	2015	Prognosis/Monitoring Disease Progression	Emotions	Video Recording		Video camera	> 30
Shyamal Patel et al. [104]	2009	Prognosis/Monitoring Disease Progression	Tremor, Movement disorder	Wearable	Video Recording	Accelerometer, Video camera	$10<n\leq 20$

Table 4.4: Papers about Diagnosis, Early Diagnosis and Differential Diagnosis

Reference	Year	Applicaton	Aspect Area	Device	Additional Device	Sensors	No of Subjects (n)
Jan Raethjen et al. [109]	2009	Diagnosis	Nerve/Brain signals, Muscle activity	Biopotential		EEG, EMG	$20 < n \leq 30$
Mitsuru Yoneyama et al. [143]	2013	Diagnosis	Gait	Wearable		Accelerometer	≤ 10
Srivani Padma G et al. [131]	2015	Diagnosis	Tremor	Other		Fiber Bragg Grating Tremor Measurement (FBGTM)	uk
Bin Zhang et al. [146]	2018	Diagnosis	Tremor	Biopotential	Wearable	Accelerometer,EMG	> 30
VF Annese et al. [3]	2018	Diagnosis	Gait,Muscle activity	Biopotential		EMG	≤ 10
A.Iu Meigal et al. [86]	2009	Diagnosis	Muscle activity	Biopotential		EMG	$10 < n \leq 20$
Johannes C Ayena et al. [6]	2015	Diagnosis	Balance	Biopotential	Smartphone	Force sensor	$20 < n \leq 30$
R Soubra et al. [126]	2018	Diagnosis	Gait	Wearable		Force sensor	uk
Raffaele Ferri et al. [43]	2012	Diagnosis	Sleep Topics	Biopotential		EMG	$20 < n \leq 30$
Heinrich Garn et al. [47]	2017	Diagnosis	Dementia	Biopotential		EEG	> 30
Yolanda Camnos-Roca et al. [25]	2018	Diagnosis	Speech Topics	Audio Recording		Microphone	> 30
Athanasios Tsanas et al. [130]	2012	Diagnosis	Speech Topics	Audio Recording		Microphone	> 30
Kotsavasiloglou C et al. [70]	2017	Diagnosis	Handwriting	Other		Touch screen	$20 < n \leq 30$
Lidia Ghosh et al. [50]	2017	Diagnosis	Cognitive Activity	Biopotential		EEG	$20 < n \leq 30$
Dung Phan et al. [107]	2018	Diagnosis	Movement disroder	Wearable		Accelerometer, Gyroscope	
M. Yokoe et al. [142]	2009	Diagnosis	Motor activity	Wearable		Accelerometer, Touch sensor	

high sensitivity and specificity for the diagnosis of RBD in PD patients. Qualitative analysis of electroencephalographic features has been applied for differential diagnosis between patients with probable Alzheimer's Disease (AD), Parkinson's Disease Dementia (PDD), or dementia with Lewy bodies (DLB). Garn et al. developed a classifier for differentiating people suffering from each of the diseases based on quantitative electroencephalography (QEEG) [47]. 25 QEEG features in 61 dementia patients were compared and classified using leave-one-out cross-validation. The classification achieved an accuracy, sensitivity, and specificity of 100% using only the QEEG features, Granger causality and the ratio of theta and beta1 band powers. These results indicate that classifiers trained with selected QEEG features can provide valuable input in distinguishing among AD, DLB or PDD patients.

Analyzing speech disorders is also a prevalent strategy for diagnosis of Parkinson's Disease. Campos-Roca et al. extracted various acoustic features from an acoustic data set of 40 healthy control and 40 PD patients [25]. He used different regularization techniques to classify the data and the results achieved very high classification accuracy rates. In another study, Tsanas et al. used 4 parsimonious subsets of 132 dysphonia features computer from an existing data set of 263 samples from 43 subjects [130]. Their goal was to test the validity of novel algorithms to detect PD. They found that the classification with the new dysphonia features was able to reach almost 99% accuracy. More non-invasive strategies for detecting PD have been developed recently. For example, Ghosh et al. developed an analysis system to obtain EEG features from the temporal lobe representing the working memory output during the memory encoding process of unknown people's face [50]. Kotsavasiloglou et al. applied a machine-learning classification approach to analyze the line-drawing performance of 24 PD patients and 20 HCs [70]. Their results showed this technique could achieve accuracy of 91% in differentiating between PD patients and HCs.

Figure 4.6 shows that the interest of research in this area has always been high and

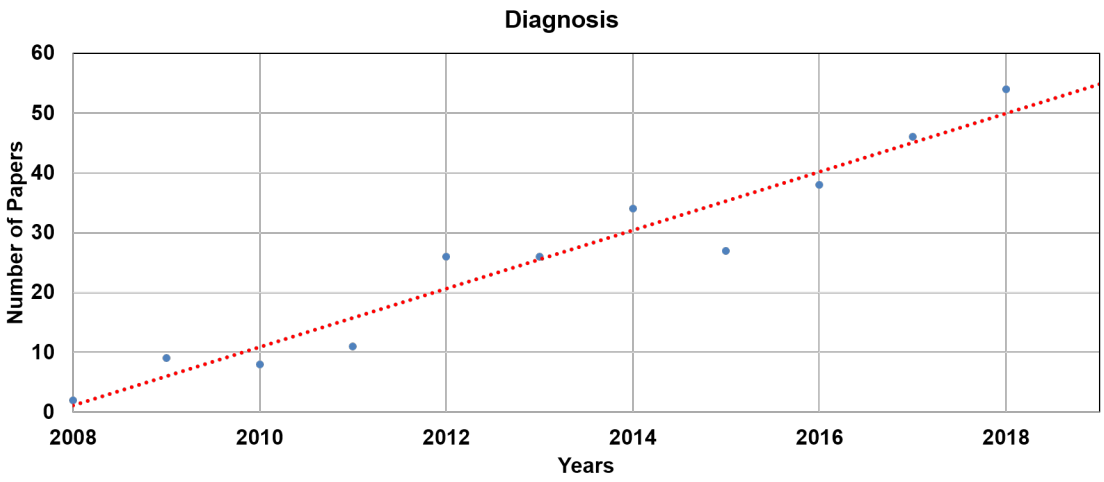

Figure 4.6: Articles published in last 10 years Focusing on Diagnosis of Parkinson's Disease.

also grew at a constant rate. Furthermore, Figure 4.11 shows that every significant device has been used in this area and audio recording devices have almost entirely been used for diagnostic purposes. Also, Figure 4.14 shows that wearable and biopotential devices are the most used device in these applications. Table 4.4 list the articles in this category and describes the classification strategy.

The development in new and portable devices along with improved algorithms have opened up new techniques of assessment of Parkinson's Disease. Advanced methods have enabled more convenient data collection for remote monitoring and tools for diagnostic aid. In the last 3 years, the number of papers that deal with the supervision of patients' symptoms and the severity of their symptoms has grown significantly. From Figure 4.7(a-d), we can observe that after 2015 the number of papers published that focus on Prognosis/-Monitoring of Parkinson's Disease Progression and Severity of Symptoms have increased at a much higher rate while the growth in the number of papers focused on other application areas have stayed at a near-constant rate. New and upcoming wearable devices have also enabled advanced rehabilitation techniques, and a lot of focus has gone in developing modern rehabilitation or symptom suppression techniques. Figure 4.7(a) shows the trend

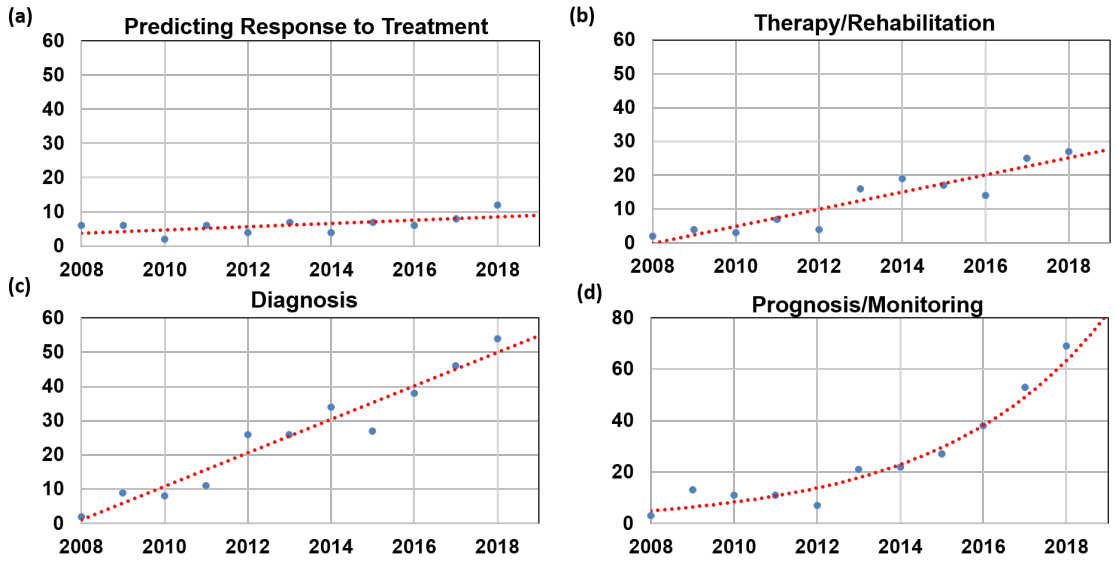

Figure 4.7: Articles published in last 10 years by PD application area. (a) Publications that are focusing on Predicting Response to Treatment, (b) Publications that are focusing on improving Therapy and Rehabilitation techniques, (c) Publications that are focusing on contributing to improving Diagnosis of PD, (d) Publications that are focusing on Prognosis and Monitoring of PD, its symptoms and assessing severity

in the number of papers that focus on validating the efficacy of a treatment plan.

It is crucial to evaluate the response of a patient to the prescribed treatment as it enables the clinician to change the dosage of medication or change the medicine altogether. But, the number of papers that focus on measuring the efficacy of a treatment plan for Parkinson's Disease using modern technologies has not grown significantly.

4.2 Measured Symptoms Included in This Study

After reviewing 778 papers, we were able to identify the major symptoms that scientific studies focus on while developing a solution for PD assessment. The symptoms are broadly classified as "Motor", "Non-motor" or "Mixed" and are listed in Table 3.2. The motor symptoms are primarily visible in a patient; thus a majority of exploration in the last

decade has been in assessing these motor symptoms like Gait disturbance, Tremor, Motor activity, Freezing of Gait, etc. Inertial data collected from IMUs used in wearable devices are widely used in monitoring gait parameters, recording tremor, motor activities, detecting FoG events, assessing bradykinesia and dyskinesia (ON/OFF Stages), etc. Force and pressure sensors placed under the shoe or in an insole sensor are used for measuring the ground reaction force, which is a popular parameter for analyzing gait. EMG sensors are used for monitoring the muscular response of a person. More sophisticated instruments like digitized tablets and smart pens are used to analyze the hand movement and pressure while writing.

Figure 3.4 shows the number of publications measuring the different motor and non-motor symptoms. Gait disturbances are prevalent in PD patients, and most studies have focused on measuring gait symptoms. It is followed by tremor and FoG which are also common symptoms of PD. Many studies have also measured movement disorders like bradykinesia and dyskinesia with the help of modern technologies. Several non-motor disabilities of PD are measure by studying the nerve/brain signals, cognitive activity, handwriting, emotion, etc. In the last 10 years, researchers have mostly focused on gait parameters and tremor for PD assessment. Figure 4.8 shows the trend in which the focus on gait and tremor has progressed in the last decade. It can be observed that following 2012 more research studies have focused on gait than tremor, even though the number of papers for each of these symptoms kept growing. With the popularity of wearables and with the development of advanced IMUs measuring of gait parameters became easier.

4.3 Most Commonly Used Devices

We investigated the 778 articles published between January 1, 2008, and December 31, 2018, and identified the major types of devices that are used in scientific research in the assessment of Parkinson's Disease and its symptoms. The primary categories as described

before are “Wearable Devices”, “Biopotential Devices”, “Cueing Devices”, “Motion Capturing Devices”, “Audio Recording”, “Video Recording”, “Force/Pressure” and “Smartphone”. Devices that did not fall under these categories were marked as “Other”. The criteria for a device to be classified under these categories are elaborated in Section 3.3.3.

Of the papers reviewed, 41% used a Wearable device for collecting the data, 20% papers used Biopotential devices, 7% used Audio Recording devices, 6% used Motion Capturing systems, 6% used different Cueing devices like auditory, haptic or visual cues. Other papers also used Video Recording devices, Smartphone, etc. Figures 3.5 and 4.9, show that the Wearable devices and Biopotential devices are the most used devices in the studies related to Parkinson’s assessment. The growth in the number of papers using Wearables or Biopotentials is shown in Figure 4.10(a-b). Biopotential devices like Electroencephalogram (EEG), Electrocardiogram (ECG), Electromyogram (EMG) and Electrooculogram (EOG) have been popular in assessing the stage of a patient who has Parkinson’s Disease.

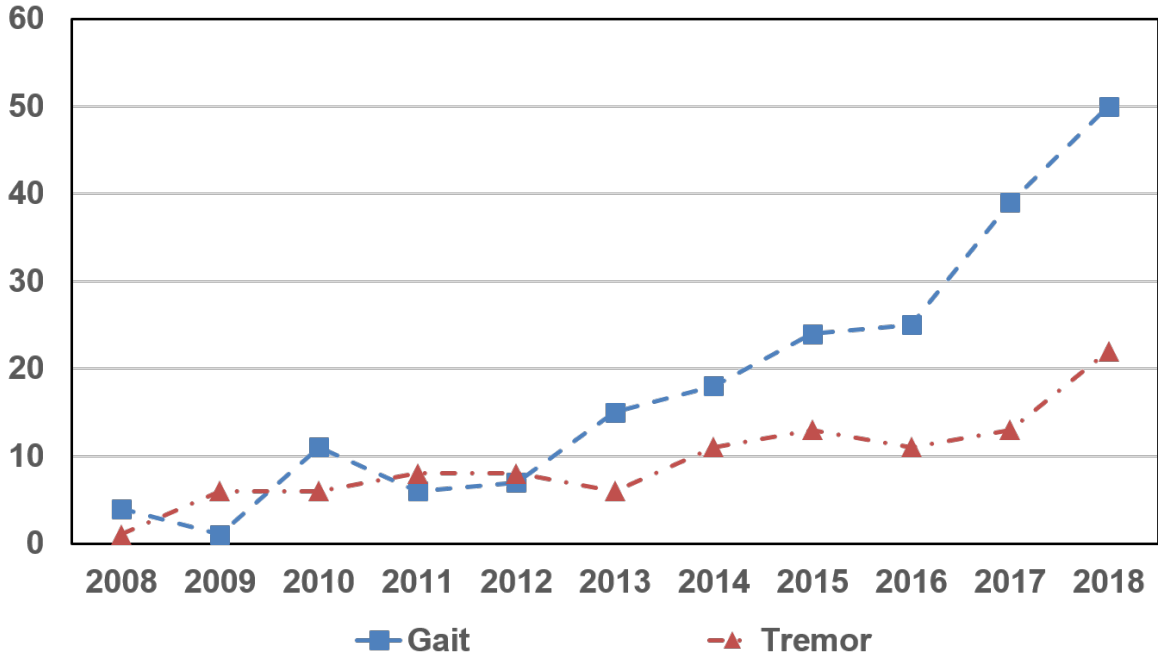

Figure 4.8: Articles published in last ten years measuring Gait or Tremor using modern technology

EEG recordings are prevalent in measuring the neural activity of a patient and is a very popular biomarker of Parkinson's Disease [109, 98, 44, 28]. EEG data is also useful for assessing other non-motor symptoms like sleep topics, dementia, cognitive activity and mixed symptoms like saccades [21, 81, 31, 132, 54, 64]. Similarly, muscular activities are also instrumental in detecting and assessing Parkinson's, and EMG recordings are beneficial in analyzing the muscle activity of a person [24, 108, 39, 4, 82]. ECG and EOG are also used by many researchers to study the heart rate and optical movements, respectively, to assess PD in patients [69, 1, 75]. Figure 4.10(a) suggests that the number of papers that use biopotential devices to evaluate PD symptoms has grown at a constant rate. With the development of portable Biopotential devices and the fact that many Wearable devices now also have Biopotential sensors like EMG and EEG, more scientists are expected to use wearable devices for PD assessment in the future.

Due to the growth in the overall interest in the assessment of Parkinson's Disease (Figure 4.2), the number of studies about the device has grown in the last decade as shown in the heat-map in Figure 4.9. In the last decade, particularly in the past 5 years, they have

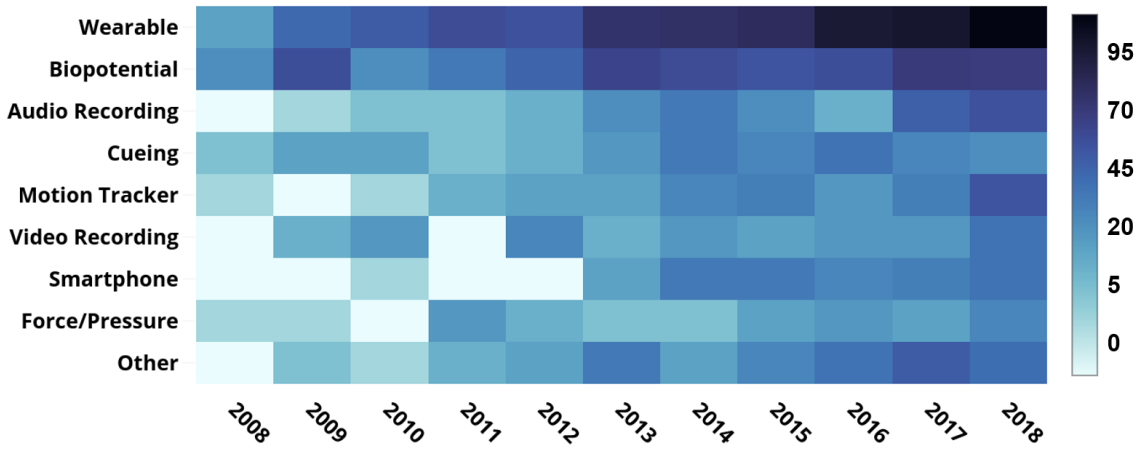

Figure 4.9: Distribution of articles published between 2008-2018 related to the assessment of Parkinson's Disease using modern technology

focused on the assessment of Parkinson's Disease with modern technologies have grown significantly. Devices like Motion Capturing systems, Audio Recording, Smartphone are being used more in the last several years and are expected to be used more in the coming future for home monitoring applications. The use of Wearable and Biopotential devices has been steadily growing in the last 10 years.

In Section 3.3.3, we have elaborated on the different devices we categorize as "Wearable". Mostly, any wireless device that can be placed on any part of a subject's body to collect some relevant data can be called a wearable device. Such devices usually have one or multiple sensors embedded in them for collecting the data, and then the raw data is either transmitted via some communication interface, i.e., Bluetooth or Zigbee, to a processing unit or is processed on a microcontroller in the device itself. Different types of sensors like accelerometer, gyroscope, magnetometer, temperature, force, pressure, etc. have been used individually or together in the research of Parkinson's assessment [57, 58, 5, 66, 140, 80, 92, 125, 88]. Wearable devices have also been developed to incorporate Biopotential

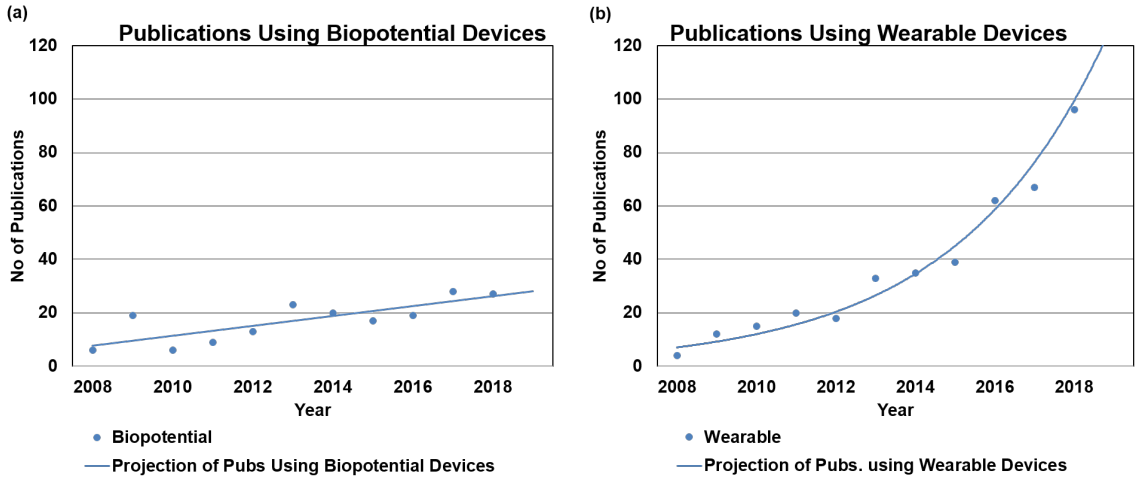

Figure 4.10: (a) The papers published between 2008 and 2018 that use Biopotential devices for PD assessment. (b) The papers published between 2008 and 2018 that use Wearable devices for PD assessment. The solid line shows the trend of the publications in the last 10 years

sensors like EMG which are used to record muscle activity data [62, 113, 146, 119, 20, 71]. Other sensors like insole force or pressure sensors have been used to evaluate the vertical ground reaction force generated when the subject is walking to assess their gait, balance or posture [147, 85, 63, 73, 97, 34, 7]. Figure 4.10(b) shows that the number of papers published using wearable devices has grown at an exponential rate in the last 10 years and is expected to keep growing. Wearable devices have been useful in all four application areas as shown in Figure 4.11.

Cueing devices have been used extensively for Therapeutic and Rehabilitation purposes. Active cueing such as vibration and auditory feedback have also been used for suppression of symptoms like FoG and tremor. Visual cues have been used by different scientific studies to develop strategies for assisting walk of PD patients [99, 9, 22]. Wireless headphones have been used to give auditory feedback to patients for improved motor activity, gait training, and balance training [9, 27, 33, 112]. Moreover, auditory and vibratory cues have been used to help a patient break out of a freeze or suppress their

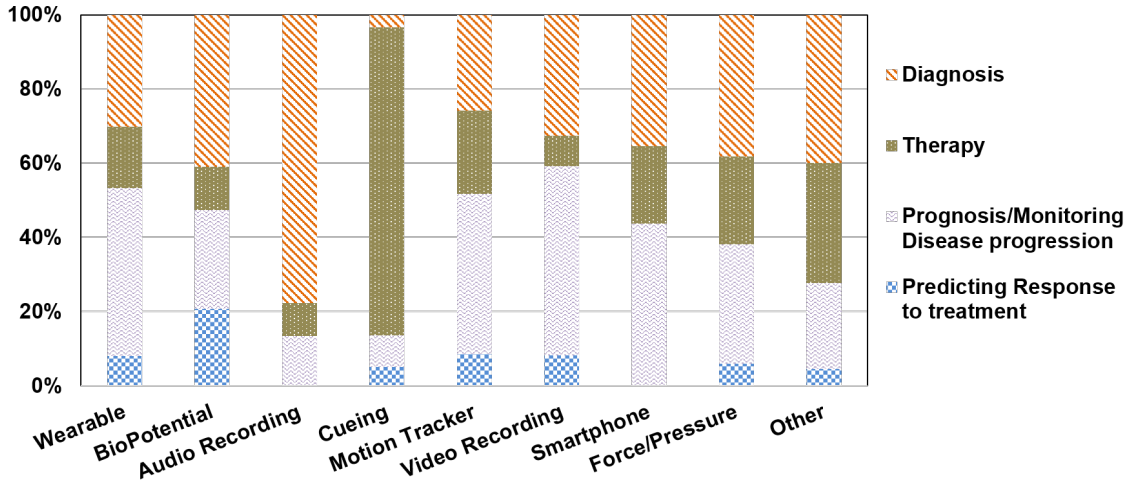

Figure 4.11: Percentage of publications between 2008-2018 using different novel technologies for PD assessment by application areas

tremor [67, 8, 77, 106, 136, 84, 26, 46]. From Figure 4.11, we can observe that around 90% of the work using cueing systems are focused on improving the therapeutic strategies and rehabilitation plans.

Audio recording devices like microphones are used to record the speech while a subject talks or perform a specific vocal task. The recorded voice sample is then analyzed to identify features that can denote the presence of Parkinson's Disease or even evaluate the severity of the disease. Figure 4.11 shows that audio recording devices are mostly used for Diagnosis or Diagnosis Aid (80%) [145, 124, 11, 148, 2, 89].

4.4 Discussion

The heat-map in Figure 4.12 shows the number of times a specific motor symptom assessed to develop a solution to a particular application area. Gait abnormality is the most popular motor symptom in PD assessment and also across all of the application areas apart from "Predicting Response to Treatment". The motor symptoms that are most commonly monitored among applications focusing on "Predicting Response to Treatment" are assessing bradykinesia and dyskinesia. They primarily monitor the ON/OFF stages and evaluate

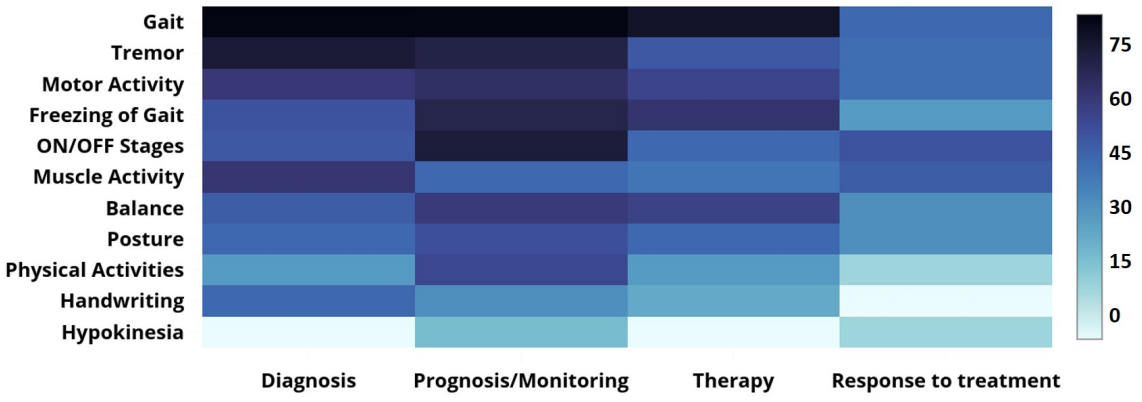

Figure 4.12: Thermal map indicating the number the publications between 2008-2018 that measure the motor symptoms of PD application areas. The darker the color, the higher the number.

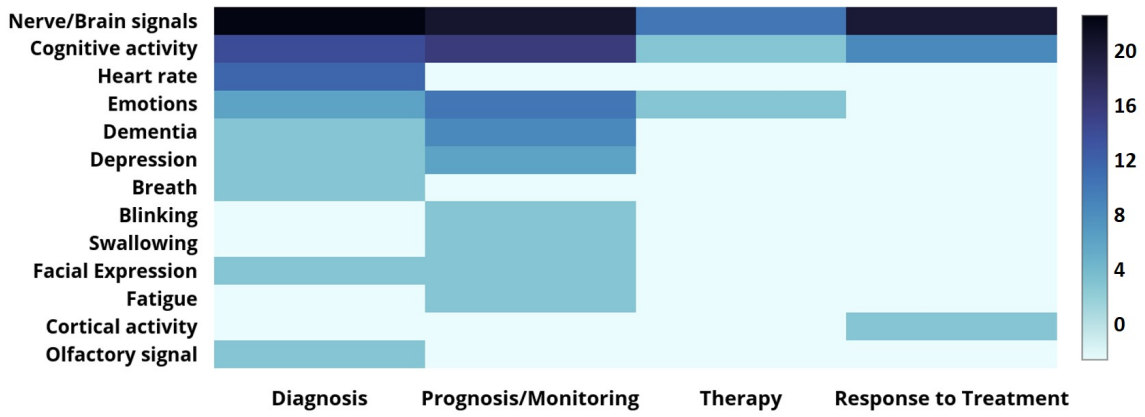

Figure 4.13: Thermal map indicating the number the publications between 2008-2018 that measure the non-motor symptoms of PD application areas. The darker the color, the higher the number.

the muscle activities. Tremor and Freezing of Gait are common motor symptoms in a PD patient and are also used as biomarkers for objective assessment of PD. Analyzing the balance and posture of a patient is a common strategy used in prognosis and therapy.

Many scientific researchers are now focusing on non-motor symptoms such as cognitive impairment, dementia, and depression. These can be more disabling for a patient and therefore, objective assessment is required. Analyzing neural response measurements is a common strategy used by clinicians and researchers for better diagnosis, monitoring and analyzing the response to treatment as shown in Figure 4.13. Analyzing the cognitive activity of patients is also a strategy used in different application areas. However, it is evident from the heat-map that the amount of work focusing on severe and disabling symptoms such as dementia, depression, fatigue, etc. is negligible compared to the motor symptoms.

Figure 4.14 shows the most used devices in different application areas. Wearable devices are the most used device in every category, except in ”Predicting Response to Treatment” where Biopotential devices are favored. Cueing devices are almost as popular as wearables in applications related to “Therapy and Rehabilitation”, also it is worth noting that a lot of Cueing devices like headphones can be placed on different parts of a patient’s

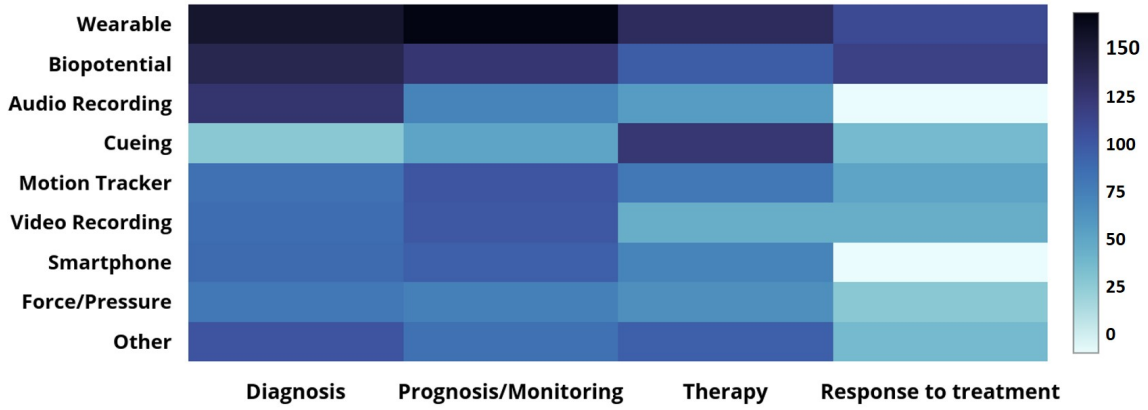

Figure 4.14: Distribution of publications between 2008-2018 related to PD assessment using modern devices, broken down by application area

body like a Wearable. Audio-recording devices are prevalent in aiding "Diagnosis" but have not been used in "Predicting Response to Treatment". Similarly, smartphones have grown in popularity in the last 5 years (Figure 4.9) but are yet to be used in applications focused on "Predicting Response to Treatment". Overall, we can observe that modern technologies are being used in all 4 areas apart from "Predicting Response to Treatment", where the total number of papers published in the last decade itself has been limited (Figure 4.7).

Chapter 5

CONCLUSIONS AND FUTURE WORK

In this review, we provided a comprehensive overview of the technological solutions currently implemented for objective assessment of Parkinson's Disease and the essential PD features. We have manually reviewed 778 articles from the last decade to identify 4 application areas, eight 8 device categories and the symptoms that are measured. This review also provided an idea of what modern technologies can afford soon. The survey can help in creating a foundation for developing future studies in this area and also for comparing their performance with similar work. This review can provide a platform to stay updated with the recent work in the field and for the scientists to compare their work with the latest development in their area. The analysis in return will educate the scientist about the performance of the novel techniques, essential features to measure, and the appropriate algorithms. Objective techniques using the necessary technologies, accompanied by the right algorithms, can aid the diagnosis and management of PD and improve the QoL of the patients. It can also bridge the gap between the technology professionals and clinicians and can assist in creating a cohort among all the contributors. From this exploratory review, we were able to judge the trend in which the studies in this field are moving. We conclude that in the scientific community, the emerging idea is to use unobtrusive systems for monitoring the progression of a disease from its nascent stage. One of the limitations of these studies are the limitations of available data sets. The small sample size of subjects a solution is tested on reduces the generalizability of the solution and also hampers its credibility. Another limitation is the optimal number and the placement of sensors. Furthermore, there are arguments among the researchers on the correct features that should be extracted from the sensor signals [117]. Lastly, for automatic assessment of the symptoms, efficient

algorithms are required to classify the symptoms with high accuracy.

Future work:

- We need to develop a tool to update our repository and to make the entire literature classification process more streamlined. Currently, we were only able to automate the filtering and identification of the papers using a Python script, while the fetching of the documents was done manually from the websites of the 4 sources mentioned in this review. In the future, we plan on using a tool that can automate this process and update our repository.

- We plan to include more databases like the Web of Science, Scopus, and Pubmed to expand our repository with other techniques and solutions used in the assessment of PD.

- A text segmentation or natural language processing-based classifier for automatic classification of the papers can increase the number of documents in our repository and include a broader range of work. It will remove the need for manual inspection of articles as shown in Figure 3.2.

- An automated classification algorithm will also enable us to inspect entire articles, not just the Title, Abstract, and Keywords. That will improve the credibility of our repository and also increase the number of documents.

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