Machine Learning Methods for Parkinson's Disease Datasets



Artur Chudzik and Andrzej W. Przybyszewski

Abstract Intelligent, dependable, and explainable computational methods for brain disease datasets remain underdeveloped and insufficiently validated, despite significant progress in machine learning (ML). Addressing this gap is crucial, as neurodegenerative diseases (NDs), such as Parkinson's disease (PD), continue to affect an increasing number of individuals. Given the challenges in managing and accurately detecting NDs, this thesis explores three approaches for data collection and analysis. Specifically, it examines diffusion tensor imaging (DTI), eye tracking, and online cognitive testing, along with selected ML algorithms designed to model PD patterns within these datasets. In the first approach, ML identified brain abnormalities through DTI analysis, detecting issues such as handwriting distortion after deep brain stimulation treatment with 82% accuracy. In the second approach, ML analyzed rapid eye movements (saccades) to identify patterns that differentiate PD patients. By combining eye-tracking data with ML algorithms, models predicted symptom development using Unified Parkinson's Disease Rating Scale (UPDRS) scores with 57–79% accuracy. In the third approach, data from web-based cognitive and behavioral tests was used to identify motor and cognitive signs of PD. Using this dataset, ML distinguished healthy controls (HC) from PD patients with 93% accuracy and mild PD from advanced PD with 80% accuracy (based on their UPDRS score). Although limited by sample size, each method provided computational insights into disease progression and helped determine PD severity based on digital data and machine learning models. Thus, the findings of this thesis contribute to the field of computer science by designing, developing, and describing digital platforms and explainable ML workflows, which are applicable to complex and limited datasets.

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H. Das et al. (eds.), *Intelligent Technologies*, Studies in Computational Intelligence 1212, https://doi.org/10.1007/978-981-96-5585-4_6

Keywords Machine learning · Digital biomarkers · Parkinson's disease · DTI · Eye-tracking · Online cognitive testing

1 Introduction

This publication summarizes a doctoral dissertation (A.C.), which is composed of previously published peer-reviewed articles [1–11]. Neurodegenerative diseases (NDs) are devastating conditions affecting millions of people around the world [12]. This makes them the leading cause of cognitive and physical disability globally [13]. The prevalence of these diseases increases with age. Thus, with the global trend toward increased life expectancy, the burden of age-related NDs is expected to rise accordingly [13]. The most common ND is Alzheimer's disease (AD), often described as a disease that impairs memory and cognitive functioning. The second most common ND is Parkinson's disease (PD), primarily associated with movement impairments.

Despite intensive efforts and considerable advances in recent decades, biomarkers research in Parkinson's disease has yielded only limited success [14]. As described in this thesis, the major reason for the difficulty in biomarker detection is the heterogeneity of PD, observable in every aspect of the disease, from pathology to clinical phenotype and disease progression, but also underdevelopment of appropriate digital screening tools [14]. This situation negatively affects the possibility of early detection of the disease.

Because of this complexity, machine learning (ML) is increasingly being applied to Parkinson's disease diagnosis and prognosis, showing potential improvements over traditional methods [15]. ML techniques, including classical models and deep learning, can analyze various data types such as brain imaging, voice recordings, facial expressions, eye movements, and clinical assessments to detect and differentiate PD. These approaches show promise in enhancing diagnostic accuracy and enabling earlier detection of this disease.

Selected ML methods demonstrate significant potential for adaptation in clinical decision-making, offering a more systematic and informed approach to PD diagnosis. However, challenges remain in translating ML models into clinical practice, including disease-specific, task-specific, and technology-specific issues [16].

Thus, ongoing research focuses on refining ML techniques and addressing current limitations to improve their effectiveness in PD diagnosis and management. This increased effectiveness is necessary because neurodegenerative diseases are not fully understood and tools to address this problem are lacking.

NDs are complex, as they are characterized by the progressive loss of neurons in specific regions of the brain [17]. Neurodegeneration often starts in localized areas of the brain and progressively spreads through interconnected regions, worsening as the disease advances [18]. This interconnection means that dysfunction in one area can lead to disruptions in others. However, individual variations in compensatory mechanisms make early detection of neurodegenerative diseases challenging.

Disturbingly, neurodegeneration can start approximately 25–30 years before any evident symptoms appear [19]. This is because compensatory processes, including changes in brain activation within function-specific networks, help maintain normal performance despite neuronal loss [20]. This compensation works until the damage exceeds a critical threshold, after which symptoms, such as tremor in PD, become apparent. Unfortunately, by this stage, many of the affected brain structures are already severely damaged.

No cure currently exists for both most common neurodegenerative diseases, namely AD and PD [21]. Existing drugs can either slow the progression of the disease or artificially compensate for neuronal loss.

1.1 Research Gap

Because NDs are extremely challenging in management, there is a gap in validation of methods that will be sensitive enough to detect and define objectively different stages of the disease [22, 23]. Intelligent, dependable, and explainable methods for disease management remain underdeveloped and insufficiently verified.

Addressing this gap is crucial, as the application of machine learning methods to Parkinson's disease datasets can enable the development of sensitive measures for screening individuals vulnerable to PD. Effectively, this screening can lead to the introduction of disease-modifying therapies, which can slow down the disease progression.

1.2 Motivation, Objective, and Contribution

Despite advancements in medical and computer science, the lack of dependable and sensitive diagnostic tools continues to slow down the progress in fight with NDs. Therefore, this dissertation is motivated by the pressing need to address the limitations in existing methodologies and to provide computable approaches for improving diagnostic accuracy and disease progression monitoring in PD.

The primary objective of this research is to design, develop, and validate ML methods that can recognize rules and patterns in complex and diverse datasets to provide reliable insights into PD diagnosis and progression. These methods offer bridging the gap between traditional diagnostic approaches and modern digital tools by incorporating techniques that are explainable, robust, and applicable in clinical settings.

The key contributions of this dissertation are as follows:

1. **Wide Data Integration**. The study integrates diverse data modalities, including diffusion tensor imaging (DTI), eye-tracking data, and online cognitive testing, to explore their potential as digital biomarkers for PD.

2. **Machine Learning Frameworks**. The research develops ML workflows created to model PD patterns in these datasets, presenting their ability to detect and classify disease severity with notable accuracy.
3. **Explainability and Validation**. A strong emphasis is placed on the explainability and validation of ML models, ensuring that the findings are interpretable and clinically relevant.
4. **Addressing Research Gaps**. By focusing on underdeveloped and insufficiently validated approaches, the study contributes to the development of sensitive tools capable of detecting early signs of PD.
5. **Practical Applications**. The findings demonstrate the feasibility of implementing ML-based digital platforms for screening, monitoring, and managing PD, contributing to advancements in neurodegenerative disease research.

Through these contributions, this research addresses critical gaps in the application of ML to neurodegenerative disease datasets, creating a foundation for future studies and clinical adoption of advanced diagnostic tools.

1.3 Hypothesis

One of the possible directions for diagnostic methods is an approach called digital biomarkers [23]. This approach uses data collected from interactions with technology like web, mobile and wearable devices to understand human behavior or cognitive function. These data points can be aggregated and analyzed, especially using machine learning, to provide deeper insights into the cognitive state of a patient. This integration of data and ML is important because models can detect subtle patterns in variables that help to define the hidden rules of the disease.

Hypothetically, digital biomarkers with machine learning are tools that can be applied to detect PD symptoms. However, knowledge about feasibility and validity of individual digital biomarkers remains extremely limited [23, 24]. Therefore, this thesis evaluates selected machine learning methods applied to Parkinson's disease datasets and presents a summary of findings.

2 Parkinson's Disease Datasets

A proper understanding of the dataset is crucial for training effective machine learning models. This section provides a brief technical background on the disease, highlighting its complexity due to overlapping symptoms with other conditions, and discusses current treatment approaches. Parkinson's disease does not have a strict biological definition and diagnostic criteria [25]. This means that there is no single, specific biomarker (e.g., detectable in the blood or cerebral-spinal fluid) which amount of can be connected to the precise and objective score of PD severity. Thus, it is important

to notice that to tell if someone has the beginning of PD or not, can be based only on clinical, hence subjective, observation. As a result, clinical diagnostic accuracy remains suboptimal, even when the disease is clinically fully manifested [26].

2.1 Disrupted Signal in Neural Networks

Parkinson's disease is primarily characterized by the loss of dopamine-producing neurons in the brain, particularly in the region called substantia nigra (SN), a critical structure in the midbrain that is part of the basal ganglia, which plays a fundamental role in movement control. The substantia nigra produces dopamine (DA), a neurotransmitter essential for smooth, coordinated muscle activity. Dopamine deficiency disrupts the basal ganglia's ability to control and coordinate movement, which is a crucial issue in PD [27].

In PD, the degeneration of dopamine-producing neurons in the substantia nigra leads to a breakdown in dopamine signaling, particularly affecting D1 and D2 receptors (Fig. 1). Different neurons have different dopamine receptors, allowing signals to travel through specific pathways, labeled D1-D5 [27]. Among these, D1 and D2

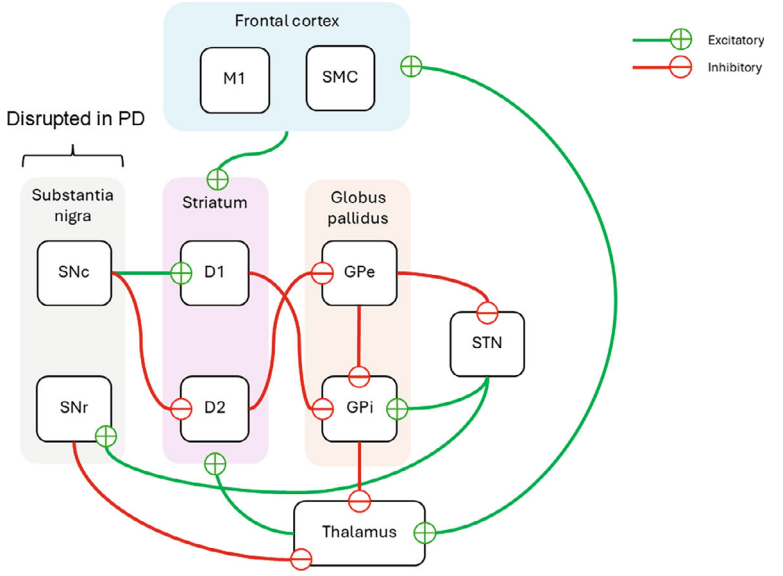


Fig. 1 Schematic representation of neural pathways disrupted in Parkinson's disease. Degeneration of dopamine-producing neurons in the substantia nigra (SNc) leads to imbalances in the GO and noGO pathways, causing excessive inhibition of the thalamus and reduced motor cortex activity. These disruptions result in motor symptoms such as bradykinesia and rigidity. Based on work by Przybyszewski et al. (2021) [28]

receptors are particularly important in the pathways that regulate movement. D1 receptors are primarily involved in the "GO" (direct) pathway, while D2 receptors participate in the "noGO" (indirect) pathway.

When dopamine levels drop, the "GO" pathway is less active, and the "noGO" pathway becomes more active [28]. This shift results in increased activity in the globus pallidus externus (GPe), which in turn increases its inhibitory effect on the subthalamic nucleus (STN). The STN, which normally excites the globus pallidus internus (GPi), is now less active, leading to reduced excitation of the GPi. Moreover, the GPi becomes less inhibited overall due to the reduced activity of the "GO" pathway. As a result, the GPi applies more inhibition to the thalamus, which weakens the signals sent back to the frontal motor cortex (FC), including areas like the primary motor cortex (M1) and the supplementary motor area (SMA). This weaker signal slows down movements.

Initially, degeneration occurs in the substantia nigra and later affects other brain structures involved in movement control and adaptability. This progression leads to the characteristic symptoms of PD, such as tremors, rigidity, bradykinesia, and postural instability. The exact cause of neuronal loss in PD is not fully understood and can vary among individuals, making it difficult to identify a single biomarker for the disease.

Neurodegenerative changes of dopaminergic pathways are not always present in the same exact region of the brain of each patient [29]. For example, neurodegeneration may begin near the SN in some cases, while in others, it may start directly within the central region of the SN. This regional variability is particularly evident across different forms of Parkinsonism, including both typical PD and its atypical variants [29].

Disrupted dopaminergic responses can be modeled artificially in computational simulations and measured using advanced imaging techniques like PET scans or fMRI [30–32]. Importantly, disrupted dopaminergic responses can be detected through digital tools like eye trackers and online cognitive testing platforms.

2.2 Overlapping Sets of Symptoms in Clinical Data

This lack of strict localization of the disease in the brain means that Parkinson's patients can have overlapping manifestations of other NDs, even including these, which are characteristic of Alzheimer's disease.

To describe these manifestations briefly, [5] distinguishes three sets of symptoms, which are related to different structures in the brain being affected by the disease. These are:

- The set of motor symptoms (observed primarily in PD, less evident in AD).
- The set of cognitive symptoms (observed primarily in AD, secondarily in PD).
- The set of emotional symptoms (observed in both, but characteristic for late-onset AD).

Cognitive impairment in Parkinson's disease is diverse and varies in its impact on different cognitive functions, and it can manifest in several ways. While there are overlapping sets of symptoms between PD and AD, they are distinct diseases with different primary manifestations and treatment approaches.

However, the overlap of these sets complicates the diagnostic process, potentially leading to misdiagnoses or delays. Therefore, neurologists must use clinical evaluations and tests to determine precisely whether and how a person is affected by these diseases. These methods will be described in detail in the next chapter.

Importantly, there is an opportunity for digital tools that can measure all these disrupted dimensions together. By simultaneously measuring the sets of cognitive, motor, and emotional symptoms, digital applications can capture the complex structure of neurodegenerative diseases through the analysis of digital traces [33]. However, in the context of machine learning, it is crucial to note that accurate prediction of symptoms brings challenges [34].

Specifically, [6] presents that when analyzing datasets, the symptoms observed in patients might be influenced by other factors, including comorbidities and individual variability in disease progression. This complexity necessitates models that can differentiate between overlapping symptoms and provide accurate predictions under these conditions.

2.3 Impact of Symptomatic Treatment on Diagnostic Data

After evaluations that led to clinical diagnosis, various treatments can support those affected by the disease. However, there is no cure for PD and AD, and only symptomatic treatment can be offered. This includes both medication and non-pharmacological approaches (such as exercise and physical, occupational, and speech therapies) [35]. One of the primary medications used is levodopa, an "early" form of dopamine.

Levodopa can be ingested and transported through the blood-brain barrier, where it is converted into dopamine in the brain, helping to replenish the depleted dopamine levels. However, dopamine-based therapies typically help with initial motor symptoms. Nonmotor symptoms require nondopaminergic approaches [35].

Other medications, such as dopamine agonists, MAO-B inhibitors, COMT inhibitors, and amantadine, can also be used to enhance or mimic dopamine's effects. Amantadine, originally used as an antiviral drug, seems to improve all cardinal motor features of PD [36, 37]. Interestingly, study [9] used a digital questionnaire for data collection and statistical analysis indicated that amantadine reduces the severity of SARS-Cov-2.

Notably, in addition to medication, treatment plans may include therapies and lifestyle changes to help manage symptoms and improve quality of life [35].

Furthermore, advanced treatments, such as deep brain stimulation (DBS), can also be considered for some patients [35]. DBS involves surgically implanting electrodes in specific areas of the brain, such as the subthalamic nucleus (STN), which is highly

connected to regions responsible for movement control, as described in "Disrupted Signal in Neural Networks" chapter. The electrodes deliver electrical impulses that modulate neural activity, emulating the effect of dopamine on the STN, and this mechanism can lead to reduction of motor symptoms. Therefore, this treatment can considerably enhance movement control in patients with Parkinson's disease.

Medical procedures like DBS require advanced digital imaging techniques [38]. Machine learning models use 3D data from MRI scans to analyze and quantify neural structures by volume and size [39]. This data provides valuable, objective input for ML models.

Lastly, in the context of data, it is important to note that patients with medicated PD may exhibit test results similar to those of healthy controls [40]. However, this similarity does not indicate the absence of PD, but rather that the therapy is effective. Consequently, this lack of clear differences makes it difficult for traditional diagnostic methods to accurately detect PD, requiring additional approaches for assessment.

2.4 Classification of Disease Progression

When measuring the progression of the disease, it has to be noted that the assessment of cognitive function in PD is complex and requires careful consideration of both the disease-specific and general aging-related factors. However, regular cognitive evaluations, both baseline and serial, are necessary to capture the wide spectrum of cognitive impairment in PD [41]. Therefore, this section serves as a summary of different rating scales, used in the context of PD.

Standard neurological examination performed by neurologists in movement disorders includes mainly two tests, namely Unified Parkinson Disease Rating Scale (UPDRS; especially Part III) and the Hoehn and Yahr scale [42–44].

3 Scales of the Disease

UPDRS is a comprehensive tool used to measure the severity and progression of Parkinson's disease [43]. Part III of this test assesses motor function, including tremor, rigidity, bradykinesia (slowness of movement), and postural instability. It involves a series of tasks that the patient performs, which are then rated by the clinician. The UPDRS is sensitive to changes over time, making it useful for tracking disease progression and evaluating treatment effects.

The Hoehn and Yahr (H&Y) is the second commonly used scale to describe the progression of Parkinson's disease in stages, ranging from Stage 1 (mild symptoms) to Stage 5 (severe disability) [42]. The scale provides a coarse categorization of disease severity.

In studies described in this thesis, neurologists provided measures of PD severity using UPDRS scale. This is because the higher granularity of the UPDRS (a wider

scale of points versus H&Y) allows for more detailed understanding of the disease progression.

3.1 Cognitive Data

Moreover, neuropsychological testing is necessary for assessment of cognitive changes in Parkinson's disease [41]. The selection and performance of these tests is not strictly standardized and can be influenced by various factors including the patient's age, educational background, language proficiency, and physical capabilities. Particularly in PD, motor impairments can complicate the assessment. Thus, it is necessary to incorporate tests that do not heavily depend on manual skill or motor speed [41].

Additionally, understanding cognitive function in PD requires insight into what constitutes normal versus pathological aging. This has to be done considering the specific motor and non-motor symptoms of PD, the effects of medical or surgical treatments, and any co-morbid neuropsychiatric complications. Therefore, cognitive function assessments in PD are conducted. This approach evaluates a range of potentially affected cognitive areas [41].

Thus, evaluations often include a combination of tests that assess global cognitive abilities and specific neuropsychological functions. These typically measure orientation, attention, executive functions, abstract reasoning, memory, language, perception, visuospatial abilities, praxis (the ability to plan and execute coordinated, purposeful movements), and motor skills [41].

However, there is no standardized method for obtaining cognitive complaints, and cognitive screening tests often lack specificity for PD. This creates a need for more normative data, particularly for individuals from lower educational or socioeconomic backgrounds.

As mentioned, standardized functional assessments are also lacking, although some PD-specific tools exist [41]. Commonly used tools for cognitive assessment include scales like Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) [41]. MoCA has proven to be more effective than some other cognitive tests [45, 46].

3.2 Behavioral and Temporal Data

Because impairment of motor control in PD is major issue, it is important to read cognitive data together with behavioral and temporal data that can provide more detailed insights into the disease [47]. This approach assumes to directly measure motor performance and its degradation.

This can be done with a few methods, including the use of multiple, so-called tracking tasks [47]. Tracking task involves visual monitoring and motor control

to complete the sequences. These tasks are designed to evaluate the precision and consistency of motor movements over time, providing insights into the progression of motor control impairment. Additionally, the integration of behavioral and temporal data with cognitive assessments allows for a comprehensive analysis of how motor and cognitive functions interact in PD.

3.3 Affected Data

Moreover, in addition to cognitive testing, it's important to evaluate other factors that might affect cognition, such as mood disorders (depression, anxiety), behavioral issues (like psychosis), sleep disturbances, and overall functional abilities. Interpretation of these elements is necessary for a complete approach to PD [41].

Mood disorders, for instance, can worsen cognitive decline and affect the patient's quality of life. Behavioral issues, such as psychosis, can complicate treatment plans and patient management. Sleep disturbances are also critical to monitor, as they can significantly impact cognitive functions and daily living activities. Assessing overall functional abilities provides insight into the patient's capability to perform everyday tasks and maintain independence. Integrating these diverse factors in datasets is required for a comprehensive approach to PD.

3.4 Multidimensional Data

Furthermore, some screening techniques can help to address multiple dimensions in a consolidated way. For example, the Trail Making Test (TMT) is a neuropsychological test that measures diverse cognitive functions, including attention, visual search and scanning, sequencing, mental flexibility, and motor speed. TMT is commonly used to evaluate cognitive function in individuals with neurological conditions. It consists of two parts: A and B.

The Trail Making Test Part A (TMT A) is a neuropsychological assessment tool primarily sensitive to processing speed and visual attention. It measures an individual's ability to rapidly connect a sequence of numbered circles in ascending order. TMT A focuses on basic scanning, attention, and motor speed.

The Trail Making Test Part B (TMT B) is a cognitive test known for its sensitivity to executive functions (involving attention, memory, visual search, motor function, and sequencing abilities). Trail B is generally more sensitive to executive functioning than TMT A since it requires multiple abilities to complete it. Using these multidimensional assessments, it is possible to identify specific cognitive deficits, but also observe how these deficits interact with each other, resulting in the degradation of motor skills and emotional well-being. Tools like the TMT can, therefore, enhance the accuracy of diagnoses.

3.5 Imaging Data

Additionally, imaging data—the test results obtained from imaging tests—are often incorporated into PD research. This data often comes from Magnetic Resonance Imaging (MRI). Imaging biomarkers in PD are increasingly important for monitoring progression in clinical trials and also have the potential to improve clinical care and management [48].

MRI scans provide 3D images of brain structures and can show specific changes in brain anatomy associated with PD. These imaging biomarkers help in tracking the progression of the disease, and even identifying early signs of neurodegeneration. Incorporating imaging data into PD research and clinical practice allows for a more precise and individualized approach to patient care.

3.6 Digital Phenotyping

With the observable progress in machine learning, digital approach and applied informatics is becoming increasingly important in neurodegenerative disease research. This is supported by research presented in [5], which confirms that machine learning and digital tools can help in the early detection of neurodegenerative diseases, potentially enabling earlier interventions that could slow disease progression.

Current research focuses on validating digital biomarkers and ML-based predictive models in identifying early-stage neurodegenerative diseases. These approaches analyze data from various sensors and computerized versions of classical tests, such as the computerized Trail Making Test (cTMT) and computerized Montreal Cognitive Assessment (cMoCA). Additionally, digital tests can measure changes in attributes related to disease phenomena, collectively referred to as the "digital phenotype." This includes analyzing facial expressions (as disturbances may suggest hypomimia, the reduction of emotional facial expression), eye movements (which can be disrupted in PD), and data from accelerometers in wearables (which can potentially detect tremors or movement disruptions).

These digital studies in NDs are conducted by multiple research groups around the world, including the Digital Biomarkers in Neurodegenerative Disease Group (nd.pja.edu.pl), an initiative started by Przybyszewski in 2018, with focus on basic and applied research for the early diagnosis of neurodegenerative diseases [49]. Recent research includes study [11], which was designed to identify AD biomarkers in healthy individuals by analyzing cognitive attributes from BIOCARD data, showing patterns indicative of potential early stages of AD. Using granular computing methods, the research predicted that some healthy subjects might develop varying degrees of dementia, validating the potential of machine learning for early AD detection and prevention.

Furthermore, Śledzianowski (2024), in his PhD thesis, demonstrated that PD progression could be observed in eye movement and facial expression properties using

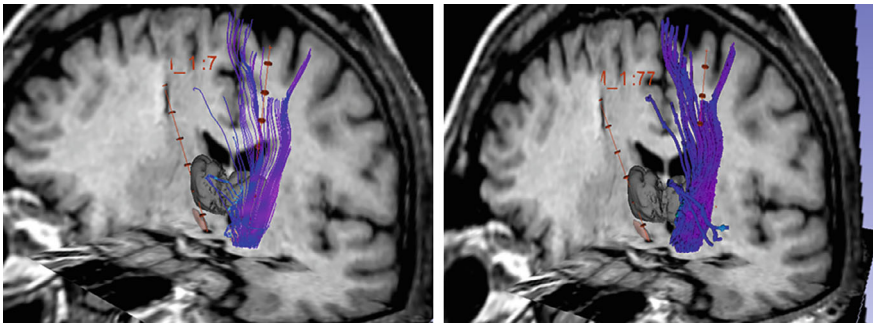


Fig. 2 Screenshot from 3DSlicer presenting a scan of a patient with exposed electrodes and neural tracts considered in the DTI study [1] showing connectivity at different DBS stimulation amplitudes

machine learning methods [50]. Earlier, Szymański (2019) explored various digital biomarkers, such as MRI/DTI imaging and local blood flow in the brain, proving their effectiveness in classifying PD symptoms, including both motor and non-motor symptoms [51]. His research also investigated the use of eye movement data for classification models, suggesting broader applications for other neurodegenerative diseases.

Collectively, these studies validate the use of digital technologies in neurodegenerative disease research and provide input for further investigation in the field, and findings described in [1–11] continue and extend research done within this group.

In summary, given the opportunities presented by previous studies in using selected methods, as well as the extreme challenge of managing and precisely detecting PD, this thesis focuses on three types of data sources: diffusion tensor imaging (DTI), eye-tracking, and online cognitive testing, along with selected ML algorithms to model the patterns in the data.

3.7 MRI and Machine Learning

Magnetic Resonance Imaging (MRI) plays a crucial role in the modern study of neurodegenerative diseases. Variations of this technique, such as Diffusion Weighted Imaging (DWI), provide insights into the structural details of the brain, allowing to visualize and quantify changes in brain anatomy and connectivity. These parameters can then be associated with diseases like Parkinson's and Alzheimer's, helping to model their progression using machine learning.

In the context of PD, an especially interesting extension of DWI is Diffusion Tensor Imaging (DTI). This approach measures the behavior of water molecules over time, including both diffusion rates and directions, represented as 3D vectors (tensors).

DTI is particularly useful in neurodegenerative diseases because it captures tractography, showing the structure of nerve tracts. This is because water molecules show greater motion along the direction of nerve fibers, thus making DTI an effective tool for mapping these structures.

Furthermore, because some treatments for PD involve invasive procedures, mapping the brain's actual structure is crucial. Deep Brain Stimulation (DBS) involves inserting a thin electrode into the brain and is often associated with post-operative complications. DTI is a non-invasive method for visualizing neural structural connectivity, making it useful for understanding the impact of electrode contacts on the brain and potentially reducing complications [52].

Detailed mapping of brain structures is complex but required for planning and executing interventions effectively and safely, and some digital tools can support this process. For example study described in [1] incorporated 3DSlicer for the registration of MRIs with an anatomical brain atlas (Fig. 2). 3DSlicer (Harvard Medical School, Boston, MA) is software platform for the visualization, processing, segmentation, registration, and analysis of medical, biomedical, and other 3D images and meshes [53]. It is peer-reviewed and a commonly used tool for planning and navigating image-guided procedures.

In the context of DBS, 3DSlicer allows for the overlay of preoperative MRI with postoperative DTI to study different pathways of connectivity between the DBS electrode and functional brain circuits. By combining these imaging modalities, it is possible to correlate stimulation parameters with the activation of specific brain structures for a more comprehensive understanding of both anatomical positioning and functional outcomes.

This approach is valuable for studying how different positions of the stimulating electrode contacts, and stimulation parameters influence brain functionality. This method differs from the traditional approach in which neurologists would assess the efficacy of DBS by observing patient symptoms over time, a process commonly referred to as "DBS tuning." However, analysis presented in [1] shows that with advanced imaging techniques it is possible to predict and study stimulation effects in a more targeted and systematic manner.

3.8 Eye Movements

Following the importance of digital imaging, eye movements emerge as another crucial aspect in the study of neurodegenerative diseases. This is because of research which shows that simple reaction times, which decline in individuals with PD, can be effectively assessed through eye movement measurements. These measurements are useful in early diagnosis, monitoring disease progression, and differentiating between PD and other cognitive impairments.

Neurodegenerative conditions like PD affect the mechanisms controlling eye movements. For example, changes in saccadic delay have been linked to changes

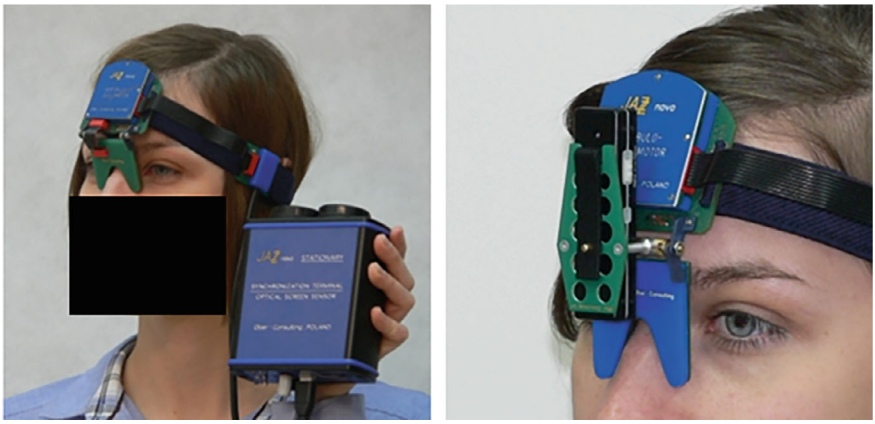


Fig. 3 Studies [3], [4] used a head-mounted saccadometer JAZZ (Ober Consulting, Poland), which was able to measure the reflexive saccades (RS) in the high frequency (1000 Hz). The advantage of this setup is lack of disruption from head movements

in the UPDRS III (motor examination), indicating that disruptions in eye movement patterns are a sign of disease progression [54].

Eye movements can be categorized into saccades, smooth pursuits, and antisaccades, each with distinct characteristics. Saccades are rapid eye movements between targets and can be divided into visually-guided (reflexive—RS) saccades, and internally-guided (voluntary). Smooth pursuit refers to the continuous movement of the eyes as they follow a moving object, and antisaccades are eye movements in the opposite direction of a suddenly appearing target. When eyes stop scanning and focus on a single point it is called fixation.

For these types of eye movements, various parameters such as delay, duration, and maximum speed can be defined and measured. They are affected by age, as eye movement efficiency improves until the early 30 s and then gradually declines [55]. Interestingly, young children and elderly individuals show worse values in eye movements, while young adults had more stable eye movement patterns (including saccades, fixations, and pursuits).

The production of saccades is a complex process that depends on the coordinated excitatory and inhibitory inputs from various cortical and subcortical structures on the brainstem, where the motor commands for saccades are finalized [56]. Dysfunction in this network impacts the delicate balance required for precise saccadic movements, leading to the characteristic eye movement abnormalities seen in neurodegenerative conditions.

These insights can be used for early detection and monitoring of neurological and cognitive disorders because eye movements are often susceptible to degradation in neurodegenerative diseases. Therefore, eye movements currently are a critical area of study in understanding and diagnosing neurodegenerative conditions such as Mild Cognitive Impairment (MCI) and Parkinson's disease [57].

Accurate measurement of eye movements requires specialized hardware and software. The most common method is video-based eye tracking, which can be performed using either specialized eye trackers or webcams. While webcams have lower frames per second (FPS) compared to dedicated eye trackers, [5] describes that they can be used with convolutional neural networks (CNN) to achieve accuracy comparable to standalone eye trackers.

As a benchmark for these approaches, outputs from more specialized devices that can capture data with high frequency often serve as a standard. Therefore, studies described in [3] and [4] used a head-mounted device with an infrared (IR) sensor, specifically the JAZZ Novo from Ober Consulting, Poland. The advantage of this setup is lack of disruption from head movements and ability to capture eye movements at 1000 frames per second, providing high frequency and precision of data (Fig. 3).

3.9 Computerized Tests

Because of the importance of not only motor but also cognitive data, and the extension of findings from eye tracking regarding the possibility to detect bradykinesia (slowness of movement) through eye movement, there is an opportunity for computerized tests that can capture not only cognitive but also motor changes using different input methods, such as cursor movements.

However, there is an ongoing discussion whether digital cognitive tools are comparable and trustworthy in the same way as their pen-and-paper equivalents. Therefore, Latendorf et al. (2021) evaluated that paper-based and digital versions of all test procedures correlated highly with each other [58]. This validity was further concluded by others, including Linari et al. who validated the computer version of TMT (cTMT) showing that the reaction times (RTs) and performance profiles are consistent with the classic TMT [59].

Moreover, Linari et al. (2022) presented an identical saccade duration, saccade amplitude, and fixation duration that suggest a similar visual mechanism between parts A and B [59]. The observed difference in the number of fixations might originate in a more complex processing of the task, more related to higher-order cognitive processes than visual mechanisms. In other words, to solve both parts of the task, subjects seem to use their visual machinery in a curiously similar way, except that TMT-B requires a more intensive scanning of the visual scene.

Interestingly, more complex tests, including digital version of Montreal Cognitive Assessment (cMoCA), require longer processing time in their pen-and-paper counterparts [58, 60]. This is related to the use of digital devices or user-friendliness because questions include tasks such as drawing a cube and a clock, which can be challenging depending on the approach used. To validate this approach, studies [6–8] describe a custom online platform to administer a group of neuropsychological tests, including computer versions of both the MoCA and the Trail Making Test (Fig. 4), along with other tests evaluating well-being and cognitive state.

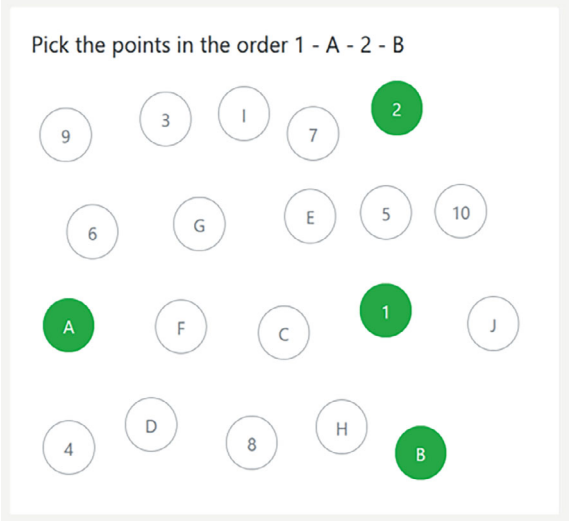


Fig. 4 The image presents a single selected screen from interactive cognitive task screen where the user is asked to pick points in a specific sequence. Web TMT B measures errors, initiation time, and execution time [8]

This custom platform incorporated additional measures, specifically both instrumental reaction time (IRT) and time-to-submit (TTS) for each task, as adding extra temporal measures to cognitive tests (such as TMT-B) can improve the accuracy of predicting UPDRS III group classification. This platform is an example of a test that integrated behavioral, temporal, and cognitive data without requiring specific hardware.

4 Models for Classification of Parkinson's Disease

To describe better the challenge of PD classification, there are two primary approaches to data modeling 5. The first most common is binary classification. This approach focuses on differentiating between individuals with Parkinson's Disease and those without (healthy controls—HC). The goal is to develop models or algorithms that can accurately classify a given individual into one of these two categories based on various types of data. The second approach involves disease stratification, determine the stage or severity of Parkinson's Disease in patients. It often involves creating models to predict disease progression or to categorize patients into different stages of the disease.

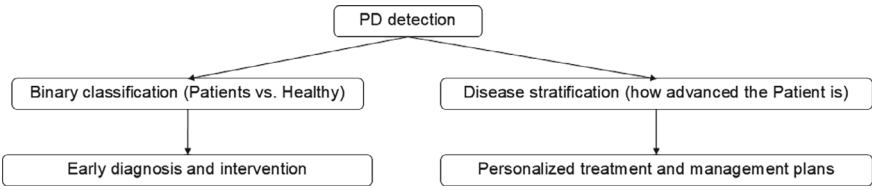


Fig. 5 The two main approaches to PD detection and their respective outcomes

4.1 Proposed Workflow

Despite differences in objectives, as well as in ML models, there is a common approach to evaluation of machine learning workflow. Importantly, managing limited datasets requires careful assessment (Fig. 6).

Therefore, the process begins with the sensor, which is able to register relevant parameters. Data from this sensor is then placed in the database, to keep the record of the patient. The next step in the workflow involves data preprocessing (profiling, cleansing, reduction, transformation, enrichment, and validation—including statistical analysis).

After confirmation that the dataset is complete, a train_test_split approach should allocate around 30% of the data for testing before modeling. This split is done randomly to ensure that 70% of subjects were used for training and 30% for testing, preventing systematic bias in the distribution.

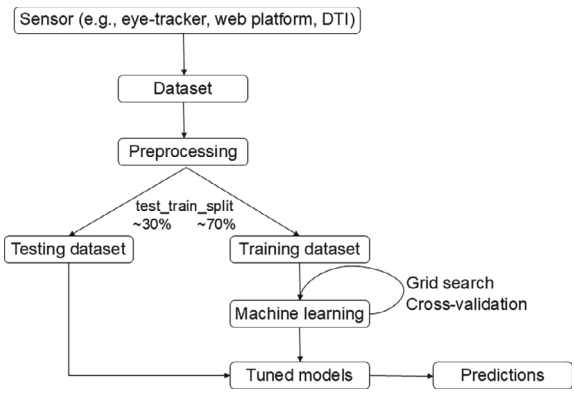


Fig. 6 Workflow for ML evaluation. Starting from sensor data collection, the workflow proceeds through data preprocessing (profiling, cleansing, reduction, transformation, enrichment, and validation). The dataset is then split into training (70%) and testing (30%) sets. Machine learning models are trained with cross-validation and grid search for hyperparameter tuning. Model-specific methods, such as regularization, are applied to prevent overfitting. The tuned models are validated using the testing dataset to generate predictions

To further mitigate the risk of overfitting, cross-validation techniques are necessary to apply during the model training phase. Thanks to this approach, it is possible to assess the model's performance more accurately and ensure its generalizability to new, unseen data.

Selected model-specific techniques can help to address the issue of overfitting. For models like Logistic Regression, [7] describes how to apply regularization methods to penalize complexity and discourage the learning of noise from the training set. This step helps to prevent overfitting, making models more robust to unseen data. The final step is the application of testing dataset on tuned models in order to validate the predictions. In practice, this workflow helps to minimize the risk of overfitting and data leakage and impacts the reliability of the results (Fig. 6).

4.2 Statistical Analysis

As presented in the workflow, the main step after dataset assembly is data preprocessing. An important part of this step includes statistical analysis. Summarizing the statistical main features of a dataset helps to review collected data. This includes calculating measures of central tendency (mean, median, mode), measures of variability (range, variance, standard deviation), and creating visual representations like histograms and charts. Testing differences between two groups by means of attributes (e.g., using t-tests, chi-square tests) provides an overview of similarities and differences between them.

Two approaches assume either using specialized software (e.g., IBM SPSS Statistics) or calculating statistics using programming languages, such as Python. Python offers open-source libraries such as Pandas for data manipulation, NumPy for numerical computations, Matplotlib and Seaborn for data visualization, and various libraries for statistical analysis [61–65].

Studies [6–8] used both approaches, combining specialized statistical software and code-based methods. Using SPSS for basic statistical analysis gives a good overview of the dataset. However, it is worth visualizing more in-depth connections between variables, for example, using Pearson's correlation coefficient, which can be calculated using Python and Pandas library. Furthermore, the Seaborn library can help to visualize these correlations in the form of a heatmap [65]. Pearson's correlation is considered an effective method for assessing associations due to its dependence on covariance, making it easily interpretable.

After processing and dividing the data, the next step is machine learning modeling. This is important because statistics are often not enough to draw conclusions from the complexity and variability seen in digital biomarkers. In essence, when statistical tests fail to find something "significant," machine learning models can start to detect more complex, nonlinear relationships that are not immediately obvious.

4.3 Machine Learning

Often when we look at data, it can be difficult to make sense of the information it contains [66]. The patterns or insights might not be immediately clear, especially if we have collected a lot of variables. In these situations, we can turn to machine learning, which is a type of technology that helps us find hidden patterns and make predictions based on the data [66]. Machine learning algorithms can analyze complex datasets and extract meaningful information that might not be obvious to the human eye.

However, conclusions have to be understandable for scientists and practitioners due to the necessity for precision medicine. Therefore, there is a need for systems that can process information in a way similar to human thinking, which often involves abstraction and dealing with incomplete information. This need drove the development of various machine learning models (function-approximation approach), and its subset of methods described by granular computing (rule-based approach).

Machine learning techniques can be broadly categorized into supervised learning, unsupervised learning, and reinforcement learning. In the context of PD research, supervised learning is often used, where the algorithm is trained on a labeled dataset, learning to make predictions or decisions based on input data. Studies [3, 4, 7, 8] employed a range of these ML techniques to model the patterns in medical data.

Primarily, ML algorithms can approximate functions that map inputs to outputs, thereby identifying patterns. This is crucial because, in computational terms, the task of PD detection can be defined as a multi-class classification problem, with the objective of predicting the disease severity level across various groups of individuals. Therefore, the following sections present the foundations of computational theory (formalization of a problem) and the selection of the best-performing algorithms, including Logistic Regression, Random Forest, and Rough Set approach.

4.4 Computational Approach

Computationally, a medical dataset consists of N training samples $(x_1, y_1), \ldots, (x_N, y_N)$, where each x_i represents the vector of features (e.g., results of tests) for the i-th sample (e.g., for each patient), and y_i is a corresponding class label (e.g., the class of disease severity).

The goal is to find a function $g : X \to Y$, which maps the input space X to the output space Y. Here, the function g belongs to a set of potential functions G, referred to as the *hypothesis space*. This is the set of all functions that the learning algorithm can choose from.

In the light of that, machine learning algorithm creates and adjusts a mapping function from input features (e.g., patient results) to output labels (e.g., medical diagnoses), using a given set of training samples. This is a non-trivial task and thus there are a couple of specific approaches to this general problem, resulting in a wide

selection of machine learning algorithms. This means however that there is no single universal solution to all machine learning problems.

The choice of model (e.g., Decision Trees, Neural Networks, Support Vector Machines, Logistic Regression, Random Forest, RSES) depends on the nature of the data and the specific characteristics of the disease patterns. Ultimately, the best-performing models can be embedded in a broader ecosystem of "artificial intelligence" (AI)—a system capable of making decisions or predictions that we perceive as "intelligent."

4.5 Optimization and Verification

Because of this challenge with model selection, there is a group of studies that focus on the analysis and the evaluation of outcomes using selected machine learning algorithms in the context of Parkinson's disease classification [67–69]. This analysis is important, because it leads to the selection of the proper tool for the prediction of PD. This comparison can be done in multiple ways.

Therefore, studies [3, 4, 7, 8] selected multiple algorithms to compare them side by side. By evaluating different models, they target to identify the most effective approach for accurately predicting disease severity and progression in PD.

A commonly used and simple metric is the accuracy of prediction. This parameter gives a fundamental overview of the performance of each classifier as it is easily understandable. Furthermore, accuracy score impacts multiple metrics as well. These other metrics, like precision, recall, F1 score, ROC (Receiver Operating Characteristic curve), and AUC (Area under the ROC curve) are often verified for better overall performance overview.

In PD, by the means of these metrics, the literature reveals that common selection of best performing algorithms includes Logistic Regression, Random Forest, Naïve Bayes, Decision Trees, K-Nearest Neighbors, Artificial Neural Networks, Support Vector Machine, and Gradient Boosting Machines [67–69].

Studies described in [3, 4, 7, 8] evaluated selected ML models, often together with granular computing approach. In the classic ML approach, the highest performance (in terms of accuracy and precision) was consistently achieved with Logistic Regression and Random Forest. However, as discussed later, these methods were often outperformed by the Granular Computing approach utilizing rough-set rules. In light of these findings, the following sections provide a brief overview of the selected algorithms.

4.6 Logistic Regression

Logistic Regression (LR) predicts categorical outcomes by modeling a linear relationship between the input variables and the log-odds of the outcome. The core of Logistic Regression is the sigmoid function, which is defined as

$$p = \frac{1}{1 + e^{-(b_0 + b_1 X)}}$$

Here, p is the probability of the positive class, b_0 represents the baseline log-odds when all predictor variables are zero (intercept term), and b_1 represents the strength and direction of the association between X and the outcome (coefficient for the predictor variable X). This formula is useful because it transforms the log-odds into output values between 0 and 1, modeling them as probabilities.

While the basic form of Logistic Regression is binary, it can be extended to manage multinomial outcomes. LR is particularly popular in healthcare analysis and medical research and yielded good results in the study [6].

4.7 Random Forest

Study [4] shows that Random Forest (RF) presents good performance in complex PD classification. The core of Random Forest are outcomes of multiple Decision Trees. Each individual tree provides a prediction based on a random subset of the data and features. In RF, the final prediction for an observation is usually obtained by aggregating the predictions from all individual trees, either by averaging (for regression tasks) or by taking the mode (for classification tasks).

Notably, Random Forest provides a metric called "feature importance" that indicates how much each feature contributes to the model's predictions, helping to identify the most influential variables in the dataset. As with Logistic Regression, the approach offered by RF is important for making informed clinical decisions and for identifying potential areas for intervention.

4.8 Granular Computing

Analysis of classical ML methods' performance versus the Rough-Set Theory (RST) described in [3] suggests that granular computing approach using rough-set rules is able to provide good predictions on medical datasets [70].

In the concept of granular computing (GrC), granules are collections of elements grouped together based on their similarity, functionality, or other criteria. These can be data points, objects, or pieces of information. Objects characterized by the same information are considered indiscernible. Any set of all similar objects forms a basic

granule (or atom) of knowledge about the universe. Each set can be described by rules that define which objects certainly belong to the set (lower approximation) and which objects "possibly" belong to the set (upper approximation). Rough Set Theory can be applied to small datasets. Moreover, generated rules often are discovered in scenarios where comprehensive models might not be feasible.

4.9 Computational Theory of Mind

In the discussion about models that can process information in a way similar to human thinking, the brain's functioning is often compared to that of a digital computer or a Universal Turing Machine, which processes symbols [71]. However, psychophysical experiments and humans' ability to recognize complex objects, such as faces, in various contexts and lighting conditions, suggest otherwise. This challenges the idea of symbolic representation and instead supports the notion that concept representation based on similarities may be a more accurate model for how the brain works.

While others interpreted principles of universal computing machine as a model of the brain, Turing himself had a different perspective on how the brain functions. Besides his development of the UTM, Turing contributed to the field of morphogenesis [72]. He proposed that natural patterns like stripes, spots, and spirals can arise from the interaction of chemical substances, which he called "morphogens." This is a process where chemicals move between cells causing them to "transform," causing the organism to develop its shape or specific pattern. This theory offers a dynamic view of biological development that contrasts with the fixed, predetermined computational process implied by the Universal Turing Machine.

Biological systems, including those studied in morphogenesis, often involve uncertain information. Rough Set Theory manages data where some information may be imprecise or missing. Therefore, [5] argues that simple rules correspond with morphogenesis principles and allow for a nuanced understanding of cognitive processes.

This comparison can be explained using visual classification tasks to understand how the brain processes information. Visual classification involves specific neural interactions, such as asynchronous process integration in the retina. The visual classification model is based on the receptive field properties of neurons in different visual areas and uses both feedforward and feedback interactions between them (Fig. 7).

In higher visual brain areas, people use processes similar to granular computing to identify upper and lower approximations of the retinal image. These approximations are compared with different object models stored in the visual cortex. As object recognition progresses, lower visual areas are tuned to extract properties of the selected model, and the gap between the upper and lower approximations narrows. When the border set becomes empty, the object is successfully recognized. This approach can be applied to propose various models that approximate the actual (and future) state of tested subjects.



Fig. 7 The receptive field properties of neurons feed into both feedforward and feedback pathways. Feedforward pathways use "driver logical rules" to create hypotheses of possible objects, while feedback pathways employ "modulator logical rules" to refine these hypotheses into crisp classifications. Higher visual brain areas then utilize GrC to compare upper and lower approximations of retinal images with stored object models, leading to object recognition as the gap between these approximations narrows [5]

Specifically, the feedforward pathways use "driver logical rules" to combine properties extracted in each area into hypotheses related to possible objects. Then, the feedback pathways use "modulator logical rules" to help transform weak concepts of objects' physical properties into crisp classifications in psychophysical space. This process approximates how the brain utilizes logical rules to transform blurred object concepts into clear categorizations.

Studies on macaques, such as those by Przybyszewski et al. (2000) show that back-projection pathways from the striate cortex (V1) to the lateral geniculate nucleus (LGN) enhance neuron responses based on visual contrast, supporting the theory of visual processing and object recognition [73]. These are connections that go from one part of the brain and back to an area that supplies input to it. Research shows that these back connections make neuron responses stronger, depending on the contrast of what is seen. Here as well, as object recognition progresses, lower visual areas are tuned to extract properties of the selected model, and the gap between the upper and lower approximations narrows (object is recognized).

This observation gives an opportunity to reconsider the algorithms we use to develop digital diagnostic tools. Insights from how biology works, as suggested by Turing's theories and recent research on xenobots (so-called "living robots"), suggest that simple rules can create a complex organism [74]. This view is maintained throughout all papers in this thesis, and it is contrary to computationally heavy, AI-driven "black box" methods.

5 Results and Contributions

The results of this research combine three distinct approaches toward data collection: using diffusion tensor imaging, eye tracking, and online cognitive testing. Each method was integrated with machine learning algorithms to analyze the data.

5.1 DTI and Machine Learning

The first study [1], ("DTI Helps to Predict Parkinson's Patient's Symptoms Using Data Mining Techniques", 2019), focused on postoperative (after DBS) patients. This approach involved ML to identify brain abnormalities through DTI analysis (Fig. 2). In this work, we conducted the analysis of RST model results and provided a detailed description of the methods and findings. The initial analysis included discovering correlations between given attributes aligned with their importance using correlation heatmap. Then, based on the obtained values, it was possible to select relevant attributes for the data mining process, performed in RSES software.

The study included three subsets of the dataset, each targeting a different UPDRS II or UPDRS III marker: "#8: handwriting distortion", "#20: tremor at rest: face, lips, chin," and "#21: action or postural tremor of hands—left hand." For each subset, we conducted experiments based on defined attributes, leading to conclusions about possible UPDRS values after DBS treatment. The results of the prediction for the left-hand tremor based on given DTI parameters revealed an accuracy of 0.967 with a coverage of 0.425. The prediction result for the "face, chin, lips tremor" achieved an accuracy of 0.824 with a coverage of 0.7. The last experiment, detecting UPDRS value changes for the "handwriting distortion," achieved an accuracy of 0.878 with a coverage of 0.667.

Using rough set rules, the model detected issues such as handwriting distortion after deep brain stimulation treatment with notable accuracy. DTI analysis focused on finding ways (connections) to determine the structure of the motor cortex depending on the stimulation parameters and contact with electrodes. This approach provided insights into specific brain microstructural changes that were different in PD patients.

Further research with independent cohorts is necessary to validate and extend these findings, because this approach provided valuable insights into disease progression and helped differentiate between PD subclasses.

5.2 Eye-Tracking and Machine Learning

The second approach involved analyzing rapid eye movements, specifically saccades, to identify patterns that differentiate PD patients. Saccades were measured using head-mounted eye-tracker (Fig. 3).

Study [2] provides analysis of this approach, and reviews various tests, using saccades, antisaccades, and pursuit, to predict disease progression using ML methods. The predictive algorithms described in the study included a range of techniques, such as granular computing, Naive Bayes, Decision Trees, Logistic Regression, C-/Linear Support Vector Classifiers, K-Nearest Neighbors Classifier, and Random Forest. The review demonstrated that by applying ML algorithms to high-dimensional eye movement data, it is possible to detect significant changes related to neurodegenerative symptoms, proposing new insights into the underlying mechanisms of these diseases.

Furthermore, in the study [3] ("Comparison of Different Data Mining Methods to Determine Disease Progression in Dissimilar Groups of Parkinson's Patients", 2020), the objective was to predict the results of different PD patients' treatments to find an optimal one. In this study we compared Rough Sets and various machine learning models, including Logistic Regression, Random Forest, Decision Tree, KNN, SVC, GradBoost, and GaussianNB, to describe and predict disease progression expressed as UPDRS values. This study showed that eye-tracking can play a crucial role in identifying different stages of PD. Because of the extensive granulation of the task, we coded the pipeline for the evaluation of ML models (Rough Sets were modeled independently), where each model was given the same task and the ability to hypertune itself in the best possible way.

When each model was prepared, they reported their scores and hypertuned parameters to analyze their behavior. This study included three groups of PD patients: 23 BMT (Best Medical Treatment) patients on medication, 24 DBS (Deep Brain Stimulation) patients on medication and DBS therapy after surgery, and 15 POP (Postoperative) patients who had undergone surgery earlier. Each patient had three visits every six months. The study estimated UPDRS changes based on disease duration, saccadic eye movement parameters, and neuropsychological tests (PDQ39 and Epworth Sleepiness Scale).

The results showed that RS rules predicted UPDRS values with global accuracies of 70% for BMT visits, 56% for DBS, and 67% and 79% for POP visits. ML models provided similar accuracy ranges, with the best performance in specific sessions. However, in contrast to RS rules, ML models could predict the results of one session (session 3—MedON) in POPW1 patients based on DBSW2 session three results. This is a limited case but shows some common mechanisms between DBS and POP groups. In this work, we were responsible for the creation and evaluation of ML models, as well as the description of the results.

This was further investigated in [4] ("Eye-Tracking and Machine Learning Significance in Parkinson's Disease Symptoms Prediction", 2020). Here, we used data of patients from the BMT group (third visit), DBS (3rd visit), and POP (1st visit). The independent test set consisted of the POP group from the second visit. Using

an upgraded version of the pipeline code for ML evaluation, we selected, hyper-tuned, and observed the behavior of ML models under this task, and we described the outcomes. In this study, by combining eye-tracking data with ML algorithms, the model achieved a 75% accuracy rate in predicting subclasses of UPDRS for patients in advanced stages of the disease.

The overall accuracy for distinguishing all classes was moderate at 57%. However, it is important to highlight that this model was designed to solve a multi-class (four-class) classification problem among dissimilar PD groups. While using fewer groups would lead to better overall accuracy, the multi-class approach provides a more granular view of the data, capturing rules among the different stages and characteristics of PD.

Despite the scores presented by these results, it is worth noting that the study was limited by sample size, which may affect the generalizability of the findings. Further research with larger cohorts is necessary to validate these results and fully establish the utility of eye-tracking as a non-invasive tool for PD diagnosis and monitoring. Nevertheless, the ML models were able to detect distinctive eye movement patterns characteristic for different stages of the disease.

5.3 Digital Cognitive Tests and Machine Learning

The newest approach involves using data from web-based cognitive tests to identify motor and cognitive signs of Parkinson's Disease. This is an outcome of the review [5] that explored digital biomarkers (tools designed for remote neurocognitive data collection and ML analysis) as a potential solution for early diagnosis of NDs. Integration of web digital tools holds a potential to transform ND diagnostics, making early detection tools more cost-effective and globally accessible.

For the evaluation of this approach, we created a web test to acquire specific motor (instrumental reaction time—IRT and time to submit—TTS) and cognitive (Trail Making Test A and B, Montreal Cognitive Assessment) data as biomarkers for disease progression. In 2023, we presented first preliminary findings of the web platform and initial model for data. Study [6] ("Investigating the Impact of Parkinson's Disease on Brain Computations: An Online Study of Healthy Controls and PD Patients", 2023), collected data from individuals with PD and healthy controls using an online platform and multiple neuropsychological tests.

Using Logistic Regression, the model achieved an accuracy rate of 91.1% in differentiating PD patients from healthy controls. However, two PD patients were misclassified as healthy subjects, and two healthy individuals were misclassified as PD patients. we also utilized multinomial Logistic Regression to predict the UPDRS III group of patients and healthy individuals, achieving similarly high accuracy. These findings suggest that web cognitive and behavioral tests can detect changes in brain computations, potentially indicating the onset of PD before clinical symptoms appear.

In the subsequent study [7] ("Classification of Parkinson's Disease Using Machine Learning with MoCA Response Dynamics", 2024), we examined the diagnostic efficiency of ML models using MoCA test results to classify scores of people with PD and healthy subjects. We implemented both rule-based modeling using Rough Set Theory and classic ML techniques such as Logistic Regression, Support Vector Machines, and Random Forests. The diagnostic accuracy of the best-performing model (RST) increased from 80.0% to 93.4%, and diagnostic specificity increased from 57.2% to 93.4% only when the MoCA score was combined with proposed temporal metrics (IRT and TTS).

This highlights that online platforms can detect subtle signs of bradykinesia (slowness of movement, a hallmark symptom of PD) and use this as a biomarker to provide more precise and specific diagnoses. Despite the constrained number of participants (15 PD patients and 16 healthy controls), the results suggest that incorporating time-based metrics into cognitive screening algorithms may significantly improve their diagnostic capabilities.

Finally, in 2024, we used the same platform to distinguish between symptoms of mild-PD and advanced-PD. In study [8] ("Recognizing Patterns of Parkinson's Disease using Online Trail Making Test and Response Dynamics - Preliminary Study", 2024), we evaluated the effectiveness of an online version of TMT A and TMT B, incorporating time-based measures to recognize cognitive and motor manifestations of PD severity. For validation, this research was conducted with 15 PD patients. The study applied TMT sensitivity to executive function impairments by measuring response and reaction times and correlating these with stages of PD severity.

We used various ML models, including Naïve Bayes, Logistic Regression, Support Vector Machine, and Random Forest, to predict disease severity based on TMT performance. Among these, Random Forest was the most effective, achieving 80% accuracy (AUC=0.92), indicating good performance in distinguishing between mild and advanced stages of PD. Although limited by sample size, this preliminary study highlights the role of digital tools in capturing specific changes in PD that can be relevant for diagnostics and monitoring of PD.

Consequently, findings from these studies present the utility of web-based platforms in assessing cognitive and motor functions in PD patients. By integrating temporal dynamics with traditional cognitive tests, we can achieve higher diagnostic accuracy and specificity.

This approach not only assists early detection but also enables continuous monitoring of disease progression in a non-invasive manner. Importantly, the results suggest that the inclusion of digital tools in routine clinical practice can support the detection and management of neurodegenerative diseases.

5.4 Research in Virtual Reality

Furthermore, it is worth noting that patients are experiencing navigation problems in 3D space in both Alzheimer's disease and Parkinson's disease. Thus, we also

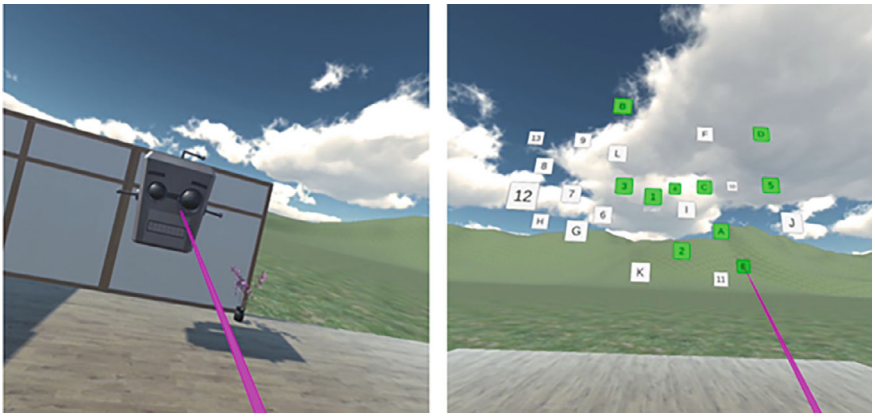


Fig. 8 The prototype of the application assessing the recognition of numbers and letters in the right order (TMT B) implemented in the VR environment on the Oculus Go device (demo online: nd.pja.edu.pl/ar-vr.html)

evaluated the possible impact of virtual reality (VR) on early disease detection as a parallel direction for diagnosis (Fig. 8).

As confirmed in web platform studies, TMT Part B is sensitive to executive functioning since the test requires multiple abilities to complete it, and thus it is more difficult in 3D. Our role in this area was to develop a prototype application for assessing the recognition of numbers and letters in the correct order within a VR environment using the Unity engine (demonstration is available online: nd.pja.edu.pl/ar-vr.html). In this context, the challenges of the virtual environment, such as cybersickness, are described in a "Further Research" section of [2]. The potential of VR technology, however, should not be dismissed.

As discussed in the referenced literature, VR applications have shown significant promise in cognitive assessments, particularly in tasks involving visuospatial processing, which is critical in the early detection of Alzheimer's disease and other neurodegenerative conditions. But accessibility issues and hardware requirements cannot be overlooked. Thus, future research should focus on optimizing these VR tools for broader clinical use, especially because it creates an immersive environment.

This is important because recent research has shown that engaging in action video games can lead to structural changes in the brain, particularly in regions associated with sensory processing, attention, and spatial navigation. Interestingly, it is possible to induce changes in gray matter thickness while playing action video games, as found in [10]. The structural plasticity of the insula could be linked to the quality of the gaming experience and the skills developed during gameplay. However, due to the additional hardware overhead required for VR, we suggest that the web approach holds promise for being more accessible by not needing dedicated hardware and software.

5.5 Summary of Contributions

In summary, our contributions to the field include the development of digital assessment platforms integrated with machine learning models for complex datasets, as well as the implementation, evaluation, analysis, and interpretation of the results.

We implemented and evaluated various ML models for the specific challenges posed by complex Parkinson's disease datasets. This work involved researching algorithms, tuning model parameters, and ensuring that the models effectively captured and predicted patterns related to disease progression.

Furthermore, we conducted a detailed analysis and interpretation of the results generated by these ML models. This included measuring performance and improving the explainability of the models, making their predictions more understandable and actionable.

A significant aspect of our contributions was the development of a web-based cognitive assessment platform designed to collect and process both cognitive and motor data from patients. This platform provided data for the ML workflow and demonstrated its capability to generate insightful datasets that register subtle changes in disease progression.

Additionally, we proposed and validated two new behavioral digital biomarkers: Instrumental Reaction Time (IRT) and Time To Submit (TTS). These biomarkers were incorporated into the assessment process and significantly enhanced the accuracy and specificity of the test results. By capturing these temporal metrics, the platform provided a more nuanced understanding of motor and cognitive impairments associated with Parkinson's disease.

Each method provided computational insights into disease progression and contributed to determining PD severity based on digital data and machine learning models. Thus, the methods described in this thesis contribute to the field of computer science through the design and development of digital platforms and explainable machine learning workflows that can be applied to complex and limited datasets, such as those related to neurodegenerative diseases.

6 Discussion

The integration of DTI, eye tracking, and online cognitive testing with machine learning ML algorithms presented the ability to draw conclusions relevant for PD diagnosis and treatment monitoring. Each method demonstrated unique strengths in identifying and predicting PD symptoms, although they are limited by sample sizes, thus requiring further research for validation, including longitudinal studies.

The study on DTI and ML focused on postoperative DBS patients, employing Rough Set Theory to predict symptoms such as tremors and handwriting distortion. The results showed high accuracy in predictions, particularly for left-hand tremors

(0.967 accuracy) and handwriting distortion (0.878 accuracy). This approach highlighted the ability of DTI to reveal brain abnormalities linked to PD and provided insights into the microstructural changes associated with the disease.

Furthermore, eye-tracking studies focused on rapid eye movements (saccades) to differentiate PD patients. By comparing various ML models and rough sets, the studies aimed to predict disease progression and treatment outcomes.

RS rules predicted UPDRS values with good accuracy, while ML models showed similar accuracy ranges and were able to predict specific session results in certain cases. A subsequent study achieved a 75% accuracy rate in predicting subclasses of UPDRS using eye-tracking data. Again, despite the promising results, the sample size again calls for further validation for the broader applicability of these findings. Nonetheless, these studies underscore the potential of eye-tracking as a non-invasive diagnostic tool for PD.

Web-based cognitive testing emerged as a powerful tool for detecting motor and cognitive signs of PD. Preliminary findings showed a high accuracy rate (91.1%) in differentiating PD patients from healthy controls using Logistic Regression. Further studies combined cognitive test scores with temporal metrics, significantly improving diagnostic accuracy and specificity. The inclusion of time-based metrics in cognitive screening algorithms highlights the potential for online platforms to capture subtle signs of PD, enabling early detection and continuous monitoring.

Additional direction explored in these studies was the use of virtual reality for the implementation of TMT B. While VR environments present challenges such as cybersickness, web-based approaches offer greater accessibility and do not require specialized hardware. Furthermore, the integration of temporal dynamics with traditional cognitive tests via web platforms can enhance diagnostic accuracy and support disease management.

In conclusion, this discussion offers a brief overview of the key points covered in articles included in this thesis. It serves as a summary of the more detailed discussions presented in each of publications, and we encourage the reader to refer to those original works for a comprehensive analysis.

7 Conclusions

This work presents the feasibility and validity of digital methods and machine learning for the detection of Parkinson's disease. While many challenges remain, the results indicate that machine learning workflows can be effectively applied to complex and limited disease datasets. This has the potential to advance the development of improved digital diagnostic approaches.

In conclusion, selected digital biomarkers combined with machine learning can be applied to detect PD symptoms in an objective and reliable manner. Further research should focus on evaluating these methods with independent samples and exploring their longitudinal application.

Author Contributions A.C. is the author of the Ph.D. thesis and prepared the manuscript. A.W.P. supervised the research and provided feedback and critical revisions.

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