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Automatic Differential diagnosis of Parkinson's Disease through multimodal techniques

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Abstract

Parkinson's disease (PD) is a neurodegenerative disorder that produces both motor and non-motor complications, degrading the quality of life of PD patients. One of the main critical problems regarding this disease is linked to the difficulty of differentiating that from other similar diseases having common symptoms. Recent advances in wearable devices technology and in machine learning, as well as in cognitive and neuropsycological studies, have provided new methods of investigating these crucial differences. The aim of this thesis is to provide a comprehensive review of current applications where a multimodal differential diagnosis have been tested, through video, movement, voice, cognitive and electrophysiological exams, in order to properly recognize and differentiate PD from atypical parkinsonism (AP) and other critical neurodegenerative syndromes, like Alzheimer's Disease (AD). This review provides the reader with a summary of the current studies and applications in the field of differential diagnosis of PD and AP, focusing on multi-modals not yet widely used but potentially promising in terms of reliability, cost and convenience. Following PRISMA (Systematic Reviews and Meta-Analyses) guidelines, fifty-six studies were selected and analyzed. For each study, information on sample size, sensors, diagnostic modes and results according to the specific symptoms under study were extracted and summarized. The majority of studies (43%) were published within the last 3 years, demonstrating the increasing focus on innovative and practical methods for a correct differential diagnosis of PD. Motor symptoms (MS) and Non-motor symptoms (NMS) were treated in equally manner, respectively 52% vs 48%, but for different types of diagnosis (the two most frequently treated were PD vs ET and DLB vs AD). Electrical sensors were the most used technology, followed by inertial and optical sensors. Finally, note that the use of machine-learning algorithms has been used in several studies. The results of this review highlight several challenges related to the use of wearable technology and cognitive/neuropsycological tests in the automatic differential diagnosis of PD, despite the advantages this technology could bring in the development and implementation of automated systems for PD assessment.

1. Introduction

The importance of differential diagnosis between Parkinson's disease (PD) and atypical parkinsonism (AP) has significantly increased over the years. Accurate differentiation is essential because, despite some overlapping symptoms, these conditions have different underlying etiopathologies, prognoses, and treatment responses. PD is characterized by the degeneration of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies, whereas AP, such as multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and corticobasal syndrome (CBS), involve more widespread neurodegeneration affecting multiple neurotransmitter systems. One major reason for the heightened focus on differential diagnosis is the impact on treatment strategies. Parkinson's disease typically responds well to dopaminergic therapies, particularly levodopa. Instead, patients with AP often show poor or limited response to these treatments. Misdiagnosis can lead to ineffective treatment plans, delayed symptom management, and unnecessary side effects from inappropriate medications. Timeliness in diagnosis is crucial because early and correct identification of the specific type of parkinsonism can guide clinicians in selecting the most appropriate therapeutic interventions and managing patient expectations. For instance, while levodopa is the cornerstone of PD treatment, managing AP might require a broader approach, including addressing autonomic dysfunction in MSA or focusing on balance and eye movement issues in PSP. Additionally, timely diagnosis allows for the implementation of supportive therapies such as physiotherapy, occupational therapy, and speech therapy tailored to the specific needs of the condition.

In this thesis work, attention is drawn to the growing number of studies concerning automatic differential diagnosis, which is therefore aimed at correctly differentiating PD, AP and related neurodegenerative diseases at the time of diagnosis, in order to make diagnosis extremely methodical and automatic. Different modes of differential diagnosis and the ways in which they are made are discussed, including some, mainly those that are potentially more efficient at the same cost and time, and excluding others.

Over the years, different and innovative diagnostic modes have been tested and developed in favour of the efficiency and convenience of diagnosis, and in favour of the patients and caregivers. Among the modes used and taken into account are those related to movement, voice, video, and cognitive and neuropsychological tests, used at different levels of complexity and in some cases even cross-referenced, making the diagnosis even more detailed.

The aim of this thesis is therefore to make a selection of the articles offered in the scientific literature in recent years in the area of the PD differential diagnosis, including certain modes. The present study reviewed articles from the period 2015 - 2023. From the aforementioned collection, the following data were extrapolated:

a. Technology used (if any): wearable devices and/or sensors used
b. Modality of diagnosis used: video, movement, voice, sleep, cognitive/neuropsychological/other tests, electrophysiological tests (EEG, ECG, EMG, etc...)
c. Parameters extracted
d. Dataset of patients
e. Algorithms and/or statistical analysis for data processing

f. Results

The paper was finally organised as follows. Chapter 2 presents the context and background of the work carried out, including a description of the pathologies involved and the associated symptomatology. Chapter 3 deals with the methods of the research, from the datasets used to the methodology with which the research was carried out, through to an exposition of the diagnoses treated and the diagnoses carried out. In Chapter 4, the results of the studies viewed are analyzed, while in Chapter 5 these are discussed. Finally, Chapter 6 has the task of providing a summary conclusion of the results found, with a look at possible future applications and possible ways forward.

2. Background

This section provides an overview of the neuropathologies analyzed in this work, from the main one, PD, to atypical and secondary parkinsonism (Sections 2.1., 2.2. and 2.3.). In addition, also related diseases having some common symptoms with the previous are described (Section 2.4.). Finally, the main symptoms, both MS and NMS, are summarized in Section 2.5.

2.1. Parkinson's disease

Idiopathic Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons in the substantia nigra, a region of the brain crucial for controlling movement. The term "idiopathic" denotes that the exact cause of this form of Parkinson's is unknown, distinguishing it from forms that have identifiable genetic or environmental causes. Parkinson's disease is one of the most common movement disorders, affecting approximately 1% of the population over the age of 60. The disease presents a complex phenomenology involving both motor and non-motor symptoms that significantly impact the quality of life of affected individuals.

Phenomenologically, PD manifests with a combination of motor symptoms, which are typically the most recognizable and early indicators of the disease. The cardinal motor symptoms include bradykinesia (slowness of movement), rigidity (muscle stiffness), resting tremor, and postural instability. Bradykinesia is often the most disabling symptom, affecting fine motor skills and overall mobility. Rigidity presents as an increased resistance to passive movement of the limbs, often leading to discomfort and pain. The characteristic resting tremor, typically starting in one hand, can progress to affect the other limbs and is usually present during rest and diminished during voluntary movement. Postural instability, which generally appears in the later stages, increases the risk of falls and associated injuries.

The non-motor symptoms of PD are diverse and can precede motor symptoms by several years. These include autonomic dysfunction (such as constipation, bladder problems, and orthostatic hypotension), sleep disturbances (including REM sleep behavior disorder and insomnia), mood disorders (such as depression and anxiety), cognitive impairment, and sensory abnormalities (like anosmia or loss of smell). These non-motor symptoms contribute significantly to the disease burden and often complicate the clinical management of PD.

The etiology of idiopathic Parkinson's disease is not well understood, but it is believed to result from a combination of genetic susceptibility and environmental factors. Although most cases of PD are sporadic, genetic factors have been implicated, with mutations in genes such as SNCA, LRRK2, and GBA being associated with an increased risk of developing the disease. Environmental factors that may contribute include exposure to pesticides, heavy metals, and other toxins, as well as head trauma. The pathological hallmark of PD is the presence of Lewy bodies, abnormal aggregates of the protein alpha-synuclein, within neurons. These aggregates disrupt cellular function and contribute to neuronal death.

Parkinson's disease progresses through several stages, each marked by increasing severity of symptoms and disability. The Hoehn and Yahr scale is commonly used to describe these stages:

Stage 1: Symptoms are mild and unilateral, affecting one side of the body. Motor symptoms, such as tremor and bradykinesia, are usually present but do not significantly impair daily activities.

Stage 2: Symptoms become bilateral, affecting both sides of the body. Although balance is still intact, daily activities may become more difficult.

Stage 3: Postural instability emerges, and although the patient is still physically independent, the risk of falls increases. Activities of daily living require more effort and time.

Stage 4: Symptoms are severe and disabling. Patients may still be able to walk or stand unassisted but require significant help with daily activities.

Stage 5: Patients are wheelchair-bound or bedridden unless assisted. They are entirely dependent on others for care.

The progression of symptoms in PD is variable and can span several years to decades. Early symptoms are often subtle and can be misattributed to normal aging or other medical conditions. The onset of motor symptoms usually prompts medical evaluation, leading to a diagnosis. However, non-motor symptoms such as constipation, anosmia, and REM sleep behavior disorder can precede motor symptoms by several years, providing potential early markers for the disease.

Diagnosing Parkinson's disease involves a comprehensive clinical assessment, as there is no definitive test for PD. The diagnosis is primarily clinical, based on the presence of cardinal motor symptoms and a thorough neurological examination. The UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria are widely used, which include the presence of bradykinesia along with one or more of the following: muscle rigidity, 4-6 Hz resting tremor, and postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction.

Neuroimaging techniques such as MRI or CT scans are often performed to rule out other causes of parkinsonism, such as stroke or brain tumors. While these scans cannot diagnose PD, they can help exclude other conditions. Dopamine transporter (DAT) scans, such as single-photon emission computed tomography (SPECT) or positron emission tomography (PET), can assess the integrity of the dopaminergic system. Reduced striatal uptake of dopamine is indicative of Parkinsonian syndromes, including PD.

The management of Parkinson's disease is multifaceted and aims to control symptoms and maintain quality of life, as there is currently no cure. Pharmacological treatment primarily involves dopamine replacement therapy. Levodopa, often combined with carbidopa to prevent peripheral conversion to dopamine, is the most effective treatment for motor symptoms. It improves bradykinesia and rigidity but may be less effective for tremor. Long-term use of levodopa can lead to motor complications such as dyskinesias (involuntary movements) and motor fluctuations (variability in motor performance).

Dopamine agonists (such as pramipexole, ropinirole, and rotigotine) mimic the effects of dopamine in the brain and can be used as initial therapy in younger patients or as adjuncts to levodopa. Monoamine oxidase-B (MAO-B) inhibitors (such as selegiline and rasagiline) and catechol-O-methyltransferase (COMT) inhibitors (such as entacapone) are used to prolong the

effects of levodopa by inhibiting its breakdown. Amantadine can be used to treat dyskinesias associated with long-term levodopa use.

Non-pharmacological therapies are also critical in managing PD. Physical therapy focuses on improving mobility, balance, and strength. Occupational therapy helps patients with daily activities, while speech therapy addresses speech and swallowing difficulties. Regular exercise has been shown to have beneficial effects on motor symptoms and overall well-being. Nutritional support is essential, particularly for managing constipation and maintaining adequate nutrition in the presence of swallowing difficulties.

Advanced PD may require more invasive treatments. Deep brain stimulation (DBS) is a surgical procedure that involves implanting electrodes in specific brain regions, such as the subthalamic nucleus or the globus pallidus internus, to modulate abnormal brain activity. DBS can significantly improve motor symptoms and reduce the need for medication, but it is not suitable for all patients and carries risks associated with surgery.

In addition to treating motor symptoms, managing non-motor symptoms is crucial. Autonomic dysfunction can be treated with medications such as fludrocortisone for orthostatic hypotension, anticholinergics for bladder dysfunction, and dietary adjustments for gastrointestinal issues. Sleep disorders may be managed with appropriate sleep hygiene practices, medications, and in some cases, cognitive-behavioral therapy. Mood disorders often require a combination of pharmacological treatment (antidepressants and anxiolytics) and psychotherapy.

The prognosis for PD varies widely among individuals. While the disease is progressive and currently incurable, advancements in treatment and supportive care have significantly improved the quality of life for many patients. Ongoing research is focused on understanding the underlying mechanisms of the disease, developing disease-modifying therapies, and identifying biomarkers for early diagnosis and monitoring disease progression.

In conclusion, idiopathic Parkinson's disease is a complex and multifaceted neurodegenerative disorder characterized by a combination of motor and non-motor symptoms. The disease progresses through several stages, each with increasing disability. Diagnosis is primarily clinical, supported by neuroimaging and other diagnostic tests to rule out other conditions. Treatment is multidisciplinary, involving pharmacological and non-pharmacological approaches to manage symptoms and improve quality of life. Ongoing research offers hope for more effective treatments and ultimately a cure for this challenging disease.

2.2. Atypical parkinsonism

Atypical parkinsonian disorders are a group of neurodegenerative diseases that share similar symptoms with idiopathic PD but have distinct pathological and clinical features. Unlike idiopathic PD, which has an unknown cause, atypical parkinsonisms have specific underlying pathologies and often do not respond well to typical PD treatments such as levodopa. These disorders include multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and dementia with Lewy bodies (DLB).

Key differences between PD and AP concern:

Pathological features: idiopathic PD primarily involves the degeneration of dopaminergic neurons with Lewy bodies in the substantia nigra. AP instead involves various types of protein accumulations (alpha-synuclein, tau) in different brain regions, leading to diverse clinical presentations.

Symptoms onset and progression: in idiopathic PD, symptoms begin asymmetrically and progress slowly over years. AP often have a more rapid progression and may present with symmetrical symptoms or a combination of parkinsonian and other neurological signs from the outset.

Response to treatment: idiopathic PD usually responds well to levodopa and other dopaminergic therapies, especially in the early stages. On the other hand, AP generally show a poor or transient response to dopaminergic medications, highlighting the need for different therapeutic strategies.

Additional symptoms: motor symptoms dominate the clinical picture, although non-motor symptoms become more prominent as the disease progresses. AP instead often present with a mix of motor and non-motor symptoms from early in the disease course, including severe autonomic dysfunction, early cognitive and prominent balance issues.

Diagnosing atypical parkinsonian disorders can be challenging due to their overlap with idiopathic PD. Early and accurate diagnosis is crucial for management and prognosis, but current clinical criteria and imaging techniques have limitations. Research is ongoing to identify biomarkers and improve diagnostic accuracy. Moreover, the lack of effective treatments for these disorders underscores the need for continued research into their pathophysiology and the development of targeted therapies.

In the following, AP are described in detail.

2.2.1. Multiple system atrophy

Multiple System Atrophy (MSA) is a rare and progressively debilitating neurodegenerative disorder that presents a complex interplay of motor, autonomic, and cerebellar symptoms. This disease typically manifests in adulthood, with the onset of symptoms usually occurring in the late 50s to early 60s. MSA is characterized by its rapid progression and poor prognosis, distinguishing it from other neurodegenerative diseases such as Parkinson's disease (PD).

The phenomenology of MSA is rooted in its diverse symptomatology, which stems from the degeneration of multiple systems within the central nervous system. The disease is divided into two primary subtypes: MSA-P, where parkinsonian features predominate, and MSA-C, where cerebellar ataxia is the leading characteristic. This classification is essential for understanding the varying clinical presentations and the underlying pathophysiological mechanisms. MSA-P typically presents with rigidity, bradykinesia, and postural instability, symptoms that closely mimic those of Parkinson's disease but often with a more rapid progression and a poorer response to dopaminergic therapy. On the other hand, MSA-C is marked by cerebellar signs such as gait and limb ataxia, dysarthria, and nystagmus, reflecting the predominant involvement of cerebellar structures.

The etiology of MSA remains largely unknown, placing it in the category of idiopathic neurodegenerative diseases. However, it is understood that MSA involves the abnormal

accumulation of alpha-synuclein protein within oligodendrocytes, cells that play a crucial role in supporting and insulating neurons. This protein aggregation leads to widespread neurodegeneration, affecting multiple neural circuits and resulting in the complex clinical picture of MSA. Unlike many other neurodegenerative conditions, there is no significant genetic predisposition associated with MSA, and familial cases are exceedingly rare. Environmental factors have been investigated, but no definitive causal links have been established.

Symptomatology in MSA is extensive and multifaceted, encompassing both motor and non-motor symptoms. Motor symptoms in MSA-P include parkinsonism, which manifests as bradykinesia, rigidity, tremor (although less prominent than in PD), and postural instability. In contrast, MSA-C is characterized by cerebellar ataxia, presenting with unsteady gait, lack of limb coordination, slurred speech (dysarthria), and involuntary eye movements (nystagmus). Non-motor symptoms are equally significant and often have a substantial impact on the patient's quality of life. Autonomic dysfunction is a hallmark of MSA, presenting early in the disease course and progressively worsening. This includes orthostatic hypotension, which causes dizziness and fainting due to a significant drop in blood pressure upon standing, as well as urinary dysfunction, such as incontinence or difficulty emptying the bladder, gastrointestinal issues like constipation and dysphagia, and sexual dysfunction.

Sleep disturbances are also prevalent in MSA, with conditions such as REM sleep behavior disorder, where patients act out their dreams, restless legs syndrome, and obstructive sleep apnea commonly reported. Cognitive impairment is less pronounced in MSA compared to other neurodegenerative disorders, but some patients do experience mild cognitive deficits, depression, and anxiety, further complicating the clinical picture.

MSA progresses through several stages, each marked by increasing severity of symptoms. In the early stage, symptoms are subtle and often misdiagnosed as other neurodegenerative diseases. Early signs might include mild motor symptoms, such as slight bradykinesia or balance issues, and minor autonomic disturbances. As the disease progresses to the middle stage, symptoms become more pronounced and diversified. Patients typically exhibit more severe parkinsonism or cerebellar ataxia, alongside significant autonomic dysfunction like urinary problems and orthostatic hypotension. In the late stage of MSA, patients experience severe disability due to extensive motor impairments, often requiring assistance for daily activities. Non-motor symptoms, especially autonomic dysfunction, can lead to life-threatening complications. The end stage of MSA is characterized by complete dependence on caregivers, with severe dysphagia and respiratory problems commonly leading to pneumonia, a frequent cause of death in these patients.

The onset and progression of symptoms in MSA are notably rapid compared to other neurodegenerative diseases. Initial symptoms typically appear in the late 50s to early 60s, with a median survival time of about 7-10 years after the onset. The early signs are often subtle and may include slight autonomic dysfunction or mild motor impairments. These symptoms rapidly progress, becoming more severe and debilitating over time.

Diagnosing MSA can be challenging due to its symptom overlap with other neurodegenerative disorders, particularly Parkinson's disease and pure autonomic failure. A comprehensive diagnostic approach is essential and involves a detailed patient history, thorough neurological examination, and various diagnostic tests. Clinical evaluation focuses

on assessing motor symptoms like parkinsonism and cerebellar ataxia, as well as autonomic functions. Imaging studies, such as MRI, can reveal characteristic changes associated with MSA, including the "hot cross bun" sign in the pons and atrophy of the putamen and cerebellum. SPECT and PET scans are also useful in assessing dopaminergic function and distinguishing MSA from Parkinson's disease.

Autonomic testing is crucial for evaluating blood pressure response to tilt-table testing, bladder function through urodynamic studies, and sweat tests to assess sudomotor function. Polysomnography, or sleep studies, can detect REM sleep behavior disorder and other sleep-related abnormalities, providing further diagnostic clues. Laboratory tests are often conducted to exclude other causes of parkinsonism and autonomic dysfunction, including blood tests and, if necessary, lumbar puncture to analyze cerebrospinal fluid.

Currently, there is no cure for MSA, and treatment focuses on managing symptoms and improving the quality of life for patients. Pharmacological treatments include medications like levodopa, which can provide temporary relief of parkinsonian symptoms, although the response is often limited. Dopamine agonists may also be used, but their effectiveness is generally less than in idiopathic Parkinson's disease. Anticholinergics can help with bladder dysfunction, while fludrocortisone and midodrine are used to manage orthostatic hypotension by increasing blood pressure. Botulinum toxin injections are sometimes employed for treating dystonia and excessive salivation.

Non-pharmacological interventions are equally important in managing MSA. Physical therapy is essential for improving mobility, balance, and strength, while occupational therapy helps patients with daily activities and improves their quality of life. Speech therapy is necessary for addressing speech and swallowing difficulties, and nutritional support is crucial for managing dysphagia and maintaining adequate nutrition. Lifestyle adjustments, such as using assistive devices for mobility, adapting the living environment to prevent falls, and regular monitoring by healthcare professionals, are vital for managing symptoms effectively.

Supportive care, including emotional and psychological support for both patients and caregivers, is also crucial. Participation in support groups and counseling can provide significant benefits in coping with the disease. Research into MSA is ongoing, with a focus on understanding the underlying pathophysiology and developing more effective treatments. Areas of interest include identifying specific biomarkers for early diagnosis and monitoring disease progression, exploring neuroprotective therapies that can protect against neuronal degeneration, investigating the potential of gene therapy to modify disease progression, and exploring the use of stem cells to replace damaged neurons and restore function.

2.2.2. Progressive supranuclear palsy

Progressive supranuclear palsy (PSP) is a rare neurodegenerative disorder characterized by a variety of motor and non-motor symptoms, which gradually worsen over time. PSP predominantly affects individuals over the age of 60 and presents a unique challenge due to its complex phenomenology, often leading to misdiagnosis, typically as Parkinson’s disease (PD). The hallmark features of PSP include difficulties with balance and walking, impaired eye movements, and a range of cognitive and behavioral changes. Understanding PSP requires a comprehensive examination of its phenomenology, etiology, symptomatology, disease progression, diagnostic techniques, and therapeutic options.

Phenomenologically, PSP is distinguished by its early and severe postural instability, which often leads to falls, usually backward. This instability, combined with stiffness and slowness of movement, mirrors some aspects of Parkinson's disease, but there are notable differences. For instance, PSP patients often exhibit more pronounced and early difficulties with vertical eye movements, specifically the inability to look downward, a symptom known as supranuclear gaze palsy. This impairment in eye movement is a critical diagnostic feature and contributes to problems with reading and navigating stairs, further exacerbating the risk of falls.

The etiology of PSP remains largely unknown, although it is classified as a tauopathy due to the abnormal accumulation of tau protein in the brain. Tau proteins are involved in stabilizing microtubules in neurons, but in PSP, these proteins become defective and form neurofibrillary tangles, disrupting cellular function. Genetic factors may play a role, although most cases of PSP are sporadic rather than familial. Mutations in the MAPT gene, which encodes the tau protein, have been associated with PSP, suggesting a genetic predisposition in some individuals. Environmental factors have also been implicated, but no definitive causative agents have been identified.

Symptomatically, PSP presents a range of motor and non-motor symptoms. Motor symptoms include bradykinesia (slowness of movement), rigidity (stiffness), and postural instability, which are similar to those seen in Parkinson's disease. However, the early onset of falls and the specific pattern of eye movement abnormalities are distinguishing features. Patients with PSP often experience dysarthria (slurred speech) and dysphagia (difficulty swallowing), which can lead to aspiration pneumonia, a common cause of death in PSP patients. These motor symptoms significantly impact daily functioning and quality of life.

Non-motor symptoms in PSP are equally debilitating and include cognitive impairment and behavioral changes. Cognitive symptoms often involve executive dysfunction, characterized by difficulties in planning, problem-solving, and multitasking. Memory loss may also occur, but it is usually less prominent than in Alzheimer's disease. Behavioral changes can include apathy, depression, and anxiety, which are common and can precede motor symptoms. Personality changes, such as increased irritability and socially inappropriate behavior, may also be observed. The combination of cognitive and behavioral symptoms often leads to significant caregiver burden and challenges in managing the disease.

PSP progresses through several stages, each marked by increasing severity of symptoms. In the early stages, patients may experience mild balance issues and subtle changes in personality or cognitive function. As the disease progresses to the middle stages, motor symptoms become more pronounced, with frequent falls, noticeable speech and swallowing difficulties, and significant eye movement abnormalities. In the advanced stages, patients are typically wheelchair-bound or bedridden, requiring full-time care. Severe cognitive impairment and behavioral issues dominate, and complications such as infections and malnutrition become prevalent.

The onset and progression of symptoms in PSP vary among individuals, but the disease typically progresses more rapidly than Parkinson's disease. The initial symptoms often include unsteady walking and frequent falls, particularly backward. As eye movement abnormalities develop, patients may report difficulty reading or performing tasks that require

looking downward. Speech and swallowing difficulties tend to emerge within a few years of symptom onset, leading to increased risk of aspiration and associated complications.

Diagnosing PSP is challenging due to its overlap with other neurodegenerative disorders, particularly Parkinson's disease and corticobasal degeneration. The diagnosis is primarily clinical, based on the presence of characteristic symptoms and a thorough neurological examination. The presence of vertical gaze palsy or slowing of vertical saccades, combined with postural instability and frequent falls within the first year of symptom onset, strongly suggests PSP. Additional supportive features include axial rigidity, dysarthria, and cognitive impairment, particularly executive dysfunction.

Neuroimaging techniques such as magnetic resonance imaging (MRI) can support the diagnosis by revealing characteristic changes in brain structure. In PSP, MRI often shows atrophy of the midbrain, which can lead to the so-called "hummingbird" or "penguin" sign on sagittal views. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) scans can assess metabolic activity and dopaminergic function, helping to differentiate PSP from Parkinson's disease. However, these imaging techniques are not definitive and are primarily used to support the clinical diagnosis.

There is currently no cure for PSP, and treatment is primarily symptomatic, aimed at improving quality of life and managing symptoms. Pharmacological treatments for PSP have limited efficacy. Dopaminergic medications, such as levodopa, which are effective in Parkinson's disease, generally provide little benefit for PSP patients. However, they may be tried in the early stages to assess any potential response. Medications to manage other symptoms, such as antidepressants for mood disorders and anticholinergics for bladder dysfunction, may be used.

Non-pharmacological therapies play a crucial role in managing PSP. Physical therapy focuses on improving balance and mobility, using exercises and assistive devices to reduce the risk of falls. Occupational therapy helps patients adapt their environment and daily activities to maintain independence for as long as possible. Speech therapy is essential for managing dysarthria and dysphagia, employing techniques to improve speech clarity and safe swallowing. Nutritional support is critical, as weight loss and malnutrition are common issues in advanced PSP. In some cases, feeding tubes may be necessary to ensure adequate nutrition and prevent aspiration.

Supportive care for PSP patients involves a multidisciplinary approach, including neurologists, physiotherapists, occupational therapists, speech therapists, and nutritionists. Palliative care is also an important aspect of managing PSP, particularly in the advanced stages, focusing on relieving symptoms and providing support to patients and their families. Education and support for caregivers are essential, as the burden of caring for a PSP patient can be substantial.

2.2.3. Dementia with Lewy bodies

Lewy body dementia (LBD) is a complex and multifaceted neurodegenerative disorder characterized by the presence of Lewy bodies—abnormal aggregates of protein that develop inside nerve cells. It is the second most common type of progressive dementia after Alzheimer's disease, and it significantly affects cognitive, motor, and behavioral functions.

Understanding LBD requires a detailed exploration of its phenomenology, etiology, symptomatology, disease stages, symptom onset, diagnostic techniques, and therapeutic approaches.

Phenomenologically, Lewy body dementia manifests through a constellation of cognitive, motor, and psychiatric symptoms that overlap with both Alzheimer's disease and Parkinson's disease. The cognitive symptoms include fluctuating levels of attention and alertness, which can vary dramatically from day to day or even hour to hour. This fluctuation is a distinctive feature of LBD and is often described by caregivers as "good days and bad days." Visual hallucinations are another hallmark symptom, often detailed and complex, involving people, animals, or objects that are not present. These hallucinations can be very distressing for patients and their families. LBD also includes severe sensitivity to antipsychotic medications, which can cause significant worsening of symptoms or even life-threatening reactions.

The etiology of Lewy body dementia involves the accumulation of alpha-synuclein proteins, which form Lewy bodies inside neurons. These protein aggregates disrupt the normal functioning of the brain, particularly affecting areas responsible for cognitive function, motor control, and regulation of mood and behavior. The exact cause of this abnormal protein accumulation is not fully understood, but it is believed to involve a combination of genetic, environmental, and possibly other factors. Genetic predispositions, such as mutations in the SNCA gene, which encodes alpha-synuclein, have been linked to LBD, although these are rare. Environmental risk factors are less well defined but may include exposure to certain toxins or head trauma.

Symptomatically, LBD presents with a blend of motor and non-motor symptoms. Motor symptoms in LBD are similar to those seen in Parkinson's disease, including bradykinesia (slowness of movement), rigidity (muscle stiffness), and tremors. However, these symptoms tend to be less severe and more variable in LBD than in classic Parkinson's disease. Additionally, LBD patients often exhibit gait disturbances and balance problems, leading to frequent falls.

Non-motor symptoms are diverse and significantly impact the quality of life. Cognitive symptoms include memory loss, impaired executive function, and difficulty with spatial awareness. Unlike Alzheimer's disease, where memory loss is predominant, LBD patients often have more pronounced problems with attention and executive function. Psychiatric symptoms, particularly visual hallucinations and delusions, are common and can occur early in the disease. Depression and anxiety are also prevalent, adding to the complexity of the clinical picture. Autonomic dysfunction, such as blood pressure fluctuations, constipation, and urinary incontinence, is another key feature, reflecting the widespread impact of the disease on the nervous system.

The progression of LBD can be divided into several stages, each marked by increasing severity of symptoms. In the early stages, cognitive fluctuations and subtle motor symptoms might be present. Patients may experience slight changes in attention, occasional visual hallucinations, and minor movement difficulties. As the disease progresses to the middle stages, these symptoms become more pronounced. Cognitive decline accelerates, hallucinations become more frequent and severe, and motor symptoms, such as stiffness and tremors, worsen. In the late stages of LBD, patients often require extensive assistance with daily activities. Severe cognitive impairment, profound motor disability, and significant

psychiatric disturbances dominate the clinical picture. Patients may become bedridden, suffer from severe autonomic dysfunction, and have difficulty swallowing, increasing the risk of aspiration pneumonia.

The onset and progression of symptoms in LBD vary widely among individuals. Initial symptoms often include subtle cognitive changes and visual hallucinations. These may be followed by motor symptoms that can be mistaken for Parkinson's disease. The hallmark cognitive fluctuations and severe sensitivity to antipsychotic medications usually become apparent as the disease progresses.

Diagnosing LBD is challenging due to its symptom overlap with other neurodegenerative disorders. A thorough clinical assessment is essential, involving a detailed medical history, neurological examination, and cognitive testing. The diagnostic criteria for LBD emphasize the presence of core features: fluctuating cognition, recurrent visual hallucinations, and parkinsonism. Supportive features, such as REM sleep behavior disorder and severe neuroleptic sensitivity, also aid in diagnosis. Neuroimaging techniques, such as MRI or PET scans, can help rule out other conditions and identify brain changes associated with LBD. MRI may show generalized atrophy, while PET scans can reveal reduced activity in the occipital lobes, which is more specific to LBD.

There is currently no cure for Lewy body dementia, and treatment focuses on managing symptoms to improve quality of life. Pharmacological treatments for LBD include cholinesterase inhibitors, such as rivastigmine, which can help with cognitive symptoms and possibly reduce hallucinations. Levodopa may be used to treat parkinsonian motor symptoms, but its effectiveness is variable, and it may exacerbate psychiatric symptoms. Because of the severe sensitivity to antipsychotic medications, these drugs are generally avoided unless absolutely necessary. If used, newer antipsychotics like quetiapine or clozapine, which have a lower risk of severe reactions, are preferred.

Non-pharmacological therapies are crucial in managing LBD. Cognitive therapy can help patients cope with cognitive deficits, while physical therapy focuses on maintaining mobility and balance. Speech therapy can address difficulties with communication and swallowing. Occupational therapy is essential for adapting the living environment to the patient's changing needs and promoting independence in daily activities. Given the high prevalence of psychiatric symptoms, psychological support for both patients and caregivers is vital. Education and support groups can help families manage the challenges of LBD and reduce caregiver burden.

Supportive care for LBD involves a multidisciplinary approach, integrating the expertise of neurologists, psychiatrists, physical therapists, occupational therapists, and speech therapists. Palliative care is also an important component, particularly in the advanced stages, focusing on symptom relief and enhancing the quality of life for both patients and their families. Addressing issues such as nutrition, hydration, and the risk of infections is critical in managing the later stages of the disease.

In summary, Lewy body dementia is a debilitating neurodegenerative disorder with a complex array of cognitive, motor, and psychiatric symptoms. The disease progresses through various stages, each characterized by worsening symptoms and increasing dependency. Diagnosis is primarily clinical, supported by neuroimaging and the identification of key features.

Treatment aims to manage symptoms and improve quality of life through a combination of pharmacological and non-pharmacological therapies. Ongoing research into the underlying mechanisms of LBD and potential disease-modifying treatments offers hope for future advancements in the management of this challenging condition.

2.2.4. Corticobasal syndrome

Corticobasal syndrome (CBS), also known as corticobasal degeneration (CBD), is a rare and complex neurodegenerative disorder that falls under the umbrella of atypical parkinsonian syndromes. CBS is characterized by a progressive decline in both motor and cognitive functions, often leading to severe disability. The syndrome's multifaceted nature makes it challenging to diagnose and manage, necessitating a comprehensive understanding of its phenomenology, etiology, symptomatology, stages, symptom progression, diagnostic techniques, and therapeutic approaches.

The phenomenology of CBS is marked by a combination of asymmetric motor symptoms and cortical deficits. The disorder typically presents in individuals around the age of 60, though onset can vary. One of the defining features of CBS is its asymmetry, meaning that symptoms often begin on one side of the body and are significantly more pronounced on that side. This asymmetry distinguishes CBS from other neurodegenerative disorders. The motor symptoms of CBS include rigidity, bradykinesia (slowness of movement), and postural instability, which are also common in Parkinson's disease. However, unlike Parkinson's disease, the motor symptoms in CBS are often accompanied by severe limb apraxia—a difficulty in performing purposeful movements despite having the physical ability to do so. This can manifest as difficulty in using tools or performing daily tasks.

The etiology of CBS is rooted in the abnormal accumulation of tau protein within brain cells. Tau is a microtubule-associated protein that stabilizes the cytoskeleton in neurons. In CBS, tau protein becomes hyperphosphorylated and aggregates into neurofibrillary tangles, leading to neuronal dysfunction and cell death. These tauopathies are primarily found in the cortex and basal ganglia, hence the name corticobasal. The exact cause of tau aggregation in CBS is not fully understood, but it is believed to involve a combination of genetic, environmental, and possibly other factors. There is some evidence suggesting a genetic predisposition, particularly involving mutations in the MAPT gene, which encodes the tau protein. However, these genetic links are not as strong or as well-defined as in other neurodegenerative disorders such as Alzheimer's disease.

The symptomatology of CBS is diverse, encompassing both motor and non-motor symptoms. The motor symptoms of CBS are primarily characterized by asymmetric limb rigidity and bradykinesia. Dystonia, or abnormal muscle contractions causing involuntary movements, is also common. These motor disturbances often lead to significant impairment in activities of daily living. Another key motor symptom is limb apraxia, where patients struggle with coordinating movements, making it difficult to carry out tasks that require sequential hand movements, such as dressing or cooking.

Non-motor symptoms in CBS are equally debilitating and include cognitive and behavioral changes. Cognitive deficits often resemble those seen in other dementias, with executive function, language, and visuospatial abilities commonly affected. Memory impairment is less prominent compared to Alzheimer's disease. Patients may also experience alien limb

phenomenon, where a limb seems to act on its own without the patient's control, which can be both disturbing and disabling. Behavioral symptoms can include apathy, depression, irritability, and changes in personality. These symptoms often add to the burden on caregivers and complicate the clinical management of the disease.

CBS progresses through several stages, each marked by worsening symptoms and increasing disability. In the early stages, the disease might present subtly, with mild motor symptoms such as occasional stiffness or slowness in one limb. Cognitive and behavioral symptoms may also begin to emerge but are often overlooked or attributed to normal aging. As the disease advances to the middle stages, motor symptoms become more pronounced and bilateral, although asymmetry usually remains. At this point, patients often struggle with daily activities due to severe limb apraxia and rigidity. Cognitive impairments, such as difficulty with problem-solving and language, become more noticeable, and behavioral changes may also intensify.

In the late stages of CBS, patients typically experience severe motor and cognitive impairments. They may become wheelchair-bound or bedridden due to extreme rigidity and bradykinesia. Communication becomes increasingly difficult, and cognitive functions continue to decline. Non-motor symptoms such as urinary incontinence and swallowing difficulties can also emerge, complicating care. The progression of CBS is relentless, and patients usually require full-time care in the advanced stages.

The onset and progression of CBS symptoms can vary significantly among individuals. Initially, the disease often presents with mild motor disturbances that are misdiagnosed as other conditions such as Parkinson's disease or stroke. As symptoms progress and new ones emerge, the distinct features of CBS become more apparent. The rate of progression is typically slow but steady, with increasing disability over several years. Cognitive and behavioral symptoms may appear later in the disease course but can also be among the initial presenting symptoms in some cases.

Diagnosing CBS is challenging due to its overlapping symptoms with other neurodegenerative disorders. A definitive diagnosis is often only possible post-mortem through neuropathological examination. However, several clinical criteria and diagnostic tools can aid in the diagnosis during life. A comprehensive clinical assessment, including a detailed medical history and neurological examination, is essential. Neuroimaging techniques, such as MRI and PET scans, can help support the diagnosis by revealing characteristic patterns of brain atrophy and metabolic changes. MRI may show asymmetrical cortical atrophy, particularly in the parietal and frontal lobes, while PET scans can detect reduced glucose metabolism in these regions.

Cerebrospinal fluid (CSF) analysis can also provide supportive evidence. Elevated levels of tau protein and decreased levels of amyloid-beta protein are indicative of tauopathies like CBS. Neuropsychological testing is crucial for assessing the extent of cognitive impairment and differentiating CBS from other dementias. Tests evaluating executive function, language, and visuospatial skills are particularly useful. In some cases, genetic testing for mutations in the MAPT gene may be considered, although this is not routine.

There is currently no cure for CBS, and treatment focuses on managing symptoms and improving quality of life. Pharmacological treatments for CBS are limited and primarily aim

to address motor symptoms. Dopaminergic medications, commonly used in Parkinson's disease, may provide some benefit for rigidity and bradykinesia, but their effectiveness is often limited and can diminish over time. Muscle relaxants and antispasmodic drugs may help alleviate dystonia and muscle stiffness. Cognitive symptoms are typically managed with medications used for other forms of dementia, such as cholinesterase inhibitors, although their efficacy in CBS is variable.

Non-pharmacological therapies are critical in managing CBS. Physical therapy is essential for maintaining mobility and preventing contractures. Exercises focusing on strength, flexibility, and balance can help mitigate the impact of motor symptoms. Occupational therapy is crucial for adapting the living environment and teaching patients strategies to cope with daily activities despite their limitations. Speech therapy can address communication difficulties and swallowing problems, which are common in the later stages of the disease.

Psychological support for both patients and caregivers is vital. Behavioral interventions can help manage symptoms such as apathy and depression. Education and support groups provide valuable resources and emotional support for families coping with CBS. As the disease progresses, palliative care becomes increasingly important. Palliative care focuses on providing relief from symptoms, improving quality of life, and supporting patients and their families through the advanced stages of the disease. This includes managing pain, addressing nutritional needs, and ensuring comfort.

2.3. Secondary parkinsonism

Secondary parkinsonism (SP) refers to a group of disorders that produce symptoms similar to those of Parkinson's disease but arise from different underlying causes. Unlike idiopathic Parkinson's disease, where the cause is unknown, secondary parkinsonism has identifiable causes such as medications, other medical conditions, or environmental factors. Understanding secondary parkinsonism is crucial for accurate diagnosis and appropriate treatment, as the management strategies may differ significantly from those used for idiopathic Parkinson's disease.

Secondary parkinsonism manifests with the classic symptoms of Parkinson's disease, including tremors, rigidity, bradykinesia (slowness of movement), and postural instability. However, these symptoms result from external or secondary causes rather than the neurodegenerative processes typical of idiopathic Parkinson's disease. The main distinguishing feature is that secondary parkinsonism is potentially reversible if the underlying cause is identified and treated.

SP can be caused by a variety of factors, including medications, other neurological disorders, metabolic conditions, toxins, and structural brain abnormalities. Here are some of the primary types:

1. **Drug-Induced Parkinsonism:** This is the most common form of secondary parkinsonism. Certain medications, particularly antipsychotics and other dopamine-blocking drugs, can induce parkinsonian symptoms. These drugs interfere with dopamine receptors in the brain, mimicking the dopamine deficiency seen in Parkinson's disease. While symptoms can be reversed by discontinuing the offending

medication, some individuals may experience persistent symptoms even after stopping the drug.

2. **Vascular Parkinsonism:** Caused by multiple small strokes (lacunar infarcts) or a single larger stroke, vascular parkinsonism results from damage to the areas of the brain responsible for movement control. It often presents with lower body symptoms, such as difficulty walking, and is less responsive to typical Parkinson's treatments. This type is more common in older adults with a history of cerebrovascular disease.
3. **Metabolic Disorders:** Conditions such as Wilson's disease (a genetic disorder causing copper accumulation in the brain) and other metabolic abnormalities can cause parkinsonian symptoms. Treating the underlying metabolic disorder can sometimes improve symptoms.
4. **Normal Pressure Hydrocefalus (NPH):** NPH is characterized by an accumulation of cerebrospinal fluid in the brain's ventricles, leading to symptoms of parkinsonism, dementia, and urinary incontinence. It is sometimes reversible with surgical intervention to drain the excess fluid.

Diagnosing secondary parkinsonism poses several challenges, especially in differentiating it from idiopathic Parkinson's disease. The main key issues derive from:

Symptoms overlap: Both secondary and idiopathic Parkinson's disease share many symptoms, making clinical differentiation difficult without thorough investigation. For example, drug-induced parkinsonism and idiopathic Parkinson's can look very similar clinically.

Variable response to treatment: Patients with secondary parkinsonism often have a poor or unpredictable response to standard Parkinson's medications, such as levodopa. For instance, vascular parkinsonism usually shows limited improvement with dopaminergic therapies, complicating treatment efforts.

Reversibility: Unlike idiopathic Parkinson's disease, which is progressive and incurable, some forms of secondary parkinsonism can be partially or fully reversed if the underlying cause is treated promptly. This potential for reversibility makes accurate diagnosis critical to avoid unnecessary treatment with Parkinson's medications.

Complex etiologies: The diverse causes of secondary parkinsonism require a comprehensive and multifaceted diagnostic approach, including detailed medical history, neurological examination, and a variety of diagnostic tests such as brain imaging, blood tests, and sometimes lumbar puncture.

Prognosis: The prognosis for secondary parkinsonism varies widely depending on the cause. For example, drug-induced parkinsonism can be reversible, while parkinsonism due to chronic traumatic encephalopathy or extensive vascular damage may lead to permanent deficits and a progressive course.

In summary, secondary parkinsonism encompasses a range of disorders that mimic the symptoms of Parkinson's disease but have distinct and often identifiable causes. Recognizing and diagnosing secondary parkinsonism is essential for providing appropriate treatment and improving patient outcomes. While some forms are reversible, others may require specific management strategies different from those used for idiopathic Parkinson's disease. Clinicians must consider the wide array of potential causes and employ a thorough diagnostic process to

distinguish secondary parkinsonism from idiopathic Parkinson's disease, ensuring that patients receive the most effective care possible.

In the following are described a little more in detail only the SP that were involved in the research.

2.3.1. Vascular parkinsonism

Vascular parkinsonism is a clinical syndrome characterized by the manifestation of parkinsonian symptoms due to cerebrovascular disease. Unlike idiopathic Parkinson's disease, which is primarily a neurodegenerative disorder, vascular parkinsonism arises from multiple small strokes or a single large stroke that affects the brain regions involved in motor control, particularly the basal ganglia. This condition is more prevalent in elderly patients with a history of stroke or other risk factors for vascular disease, such as hypertension, diabetes, and atherosclerosis.

Phenomenologically, vascular parkinsonism presents with many of the same motor symptoms observed in idiopathic Parkinson's disease, including bradykinesia, rigidity, and postural instability. However, there are some distinguishing features. Patients with vascular parkinsonism often exhibit lower body parkinsonism, which is characterized by gait disturbances, difficulty initiating walking, and a higher propensity for falls. Tremor, which is a hallmark of idiopathic Parkinson's disease, is less common and typically milder in vascular parkinsonism. Additionally, these motor symptoms are frequently symmetrical, contrasting with the asymmetrical onset seen in idiopathic Parkinson's disease.

The etiology of vascular parkinsonism is directly linked to cerebrovascular events. Small vessel disease, which leads to lacunar infarcts, and large vessel disease, resulting in significant strokes, can both contribute to the development of this condition. The damage caused by these strokes disrupts the normal functioning of the basal ganglia and other areas critical for movement regulation. Risk factors such as hypertension, diabetes, hyperlipidemia, and smoking significantly increase the likelihood of cerebrovascular incidents, thereby elevating the risk of developing vascular parkinsonism.

Symptomatically, vascular parkinsonism encompasses both motor and non-motor symptoms. Motor symptoms include bradykinesia, rigidity, postural instability, and gait disturbances, particularly shuffling steps and difficulty turning. Non-motor symptoms can be varied and may include cognitive impairment, mood disorders like depression, and urinary incontinence. Cognitive decline is more pronounced and occurs earlier in vascular parkinsonism compared to idiopathic Parkinson's disease. The presence of these non-motor symptoms, especially cognitive and mood disturbances, can significantly impact the patient's quality of life and complicate the clinical picture.

The progression of vascular parkinsonism can be divided into several stages, though it does not follow a strict linear progression as seen in idiopathic Parkinson's disease. Initially, patients may experience subtle gait disturbances and mild bradykinesia. As the disease progresses, these symptoms become more pronounced, and patients may develop significant difficulty with ambulation and an increased risk of falls. In advanced stages, severe motor impairment and profound cognitive decline can occur, leading to considerable disability and dependency.

Symptoms of vascular parkinsonism can manifest abruptly following a stroke or insidiously as a result of chronic cerebrovascular insufficiency. The onset is often linked to a history of cerebrovascular events, and patients might recall episodes of transient ischemic attacks or minor strokes preceding the development of parkinsonian symptoms. The abrupt onset of symptoms following a stroke is a distinguishing feature that can aid in the differentiation from idiopathic Parkinson's disease, which typically has a more gradual onset.

Diagnostically, vascular parkinsonism requires a comprehensive evaluation that includes a detailed medical history, neurological examination, and neuroimaging studies. Brain MRI is a critical diagnostic tool, as it can reveal the presence of infarcts or extensive white matter lesions consistent with small vessel disease. These imaging findings, when correlated with clinical symptoms, can support the diagnosis of vascular parkinsonism. Additionally, neuropsychological testing may be employed to assess the extent of cognitive impairment, and vascular risk factors should be thoroughly evaluated and managed.

The treatment of vascular parkinsonism involves a multifaceted approach that addresses both the parkinsonian symptoms and the underlying cerebrovascular disease. Pharmacological treatment with dopaminergic medications, such as levodopa, is often less effective in vascular parkinsonism compared to idiopathic Parkinson's disease. Nonetheless, some patients may experience partial benefit, and a trial of dopaminergic therapy can be considered. Antiplatelet agents, antihypertensives, and statins are essential components of the treatment regimen to manage the vascular risk factors and prevent further cerebrovascular events. Physical therapy plays a crucial role in managing gait disturbances and improving mobility, while occupational therapy can assist patients in maintaining independence in daily activities.

In addition to medical and rehabilitative interventions, lifestyle modifications are important in the management of vascular parkinsonism. Patients should be encouraged to adopt a heart-healthy diet, engage in regular physical activity, and avoid smoking. Control of comorbid conditions, such as hypertension and diabetes, is critical to reduce the risk of further cerebrovascular events and slow the progression of the disease.

2.3.2. Normal pressure hydrocephalus

Normal pressure hydrocephalus (NPH) is a neurological condition characterized by the accumulation of cerebrospinal fluid (CSF) in the brain's ventricles, leading to enlargement and compression of surrounding brain tissue. Unlike other forms of hydrocephalus, the hallmark feature of NPH is that the pressure of CSF within the brain remains within the normal range despite the accumulation of fluid. This condition primarily affects older adults, typically individuals over the age of 60, and its prevalence increases with age.

The etiology of normal pressure hydrocephalus remains incompletely understood, but several factors are believed to contribute to its development. One proposed mechanism involves impaired CSF absorption due to age-related changes in the arachnoid villi, structures responsible for CSF drainage. Additionally, conditions such as subarachnoid hemorrhage, meningitis, or head trauma may predispose individuals to NPH by disrupting normal CSF circulation or absorption pathways.

Clinically, NPH is characterized by a triad of symptoms: gait disturbances, cognitive impairment, and urinary incontinence. Gait disturbances typically manifest as a wide-based,

shuffling gait with difficulties initiating steps and maintaining balance. Patients may also experience bradykinesia and difficulty with turning, resulting in a characteristic "magnetic" or "magnet gait." Cognitive impairment in NPH often presents as executive dysfunction, including problems with attention, planning, and problem-solving. Urinary incontinence may vary in severity, ranging from mild urgency to complete loss of bladder control.

The progression of NPH can be divided into several stages based on symptom severity and functional impairment. In the early stages, patients may experience subtle gait abnormalities and cognitive changes, which are often overlooked or attributed to aging. As the condition progresses, gait disturbances become more pronounced, leading to an increased risk of falls and mobility limitations. Cognitive deficits may worsen, interfering with daily activities and impairing overall quality of life. In advanced stages, severe motor and cognitive impairment may result in significant disability and dependency on caregivers for activities of daily living.

Diagnosing NPH requires a combination of clinical evaluation and neuroimaging studies. Magnetic resonance imaging (MRI) of the brain is the primary diagnostic modality, allowing visualization of ventricular enlargement and assessing the integrity of brain structures. Additionally, lumbar puncture (LP) may be performed to measure CSF pressure and obtain samples for analysis. A characteristic finding in NPH is elevated CSF pressure with normal composition, confirming the diagnosis of normal pressure hydrocephalus.

Treatment of NPH often involves surgical intervention aimed at restoring normal CSF dynamics and relieving symptoms. The most common surgical procedure for NPH is ventriculoperitoneal (VP) shunt placement, where a catheter is inserted into the brain's ventricles to divert excess CSF into the abdominal cavity, where it can be absorbed. Shunt surgery has been shown to improve gait disturbances, cognitive function, and urinary incontinence in many patients with NPH. However, not all patients may experience significant improvement, and careful patient selection is crucial to optimize outcomes.

2.4. Other related neurological disorders

In addition to all the pathologies treated so far, which can be traced back to PD, a small number of neuropathologies that have been analyzed, some more, some less, in the current review work are considered below. In particular, it should be noted that Alzheimer's disease is often analyzed in the differential diagnosis with dementia with Lewy bodies.

2.4.1. Alzheimer’s disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory loss, and functional impairment. The pathophysiology of AD involves the accumulation of abnormal protein aggregates in the brain, including beta-amyloid plaques and tau tangles, leading to synaptic dysfunction, neuronal loss, and ultimately, brain atrophy.

The clinical presentation of AD varies depending on the stage of the disease. In the early stages, individuals may experience subtle memory lapses and difficulty with word finding or performing familiar tasks. As the disease progresses, cognitive deficits worsen, affecting multiple domains such as attention, language, executive function, and visuospatial skills. Behavioral and psychological symptoms, including depression, agitation, and psychosis, may also occur in later stages of the disease.

The exact cause of AD is not fully understood, but genetic and environmental factors are believed to play a role. Mutations in genes such as amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2) are associated with familial forms of AD. Additionally, age, family history, cardiovascular risk factors, and lifestyle factors such as diet and exercise may contribute to the development of sporadic AD.

AD manifests primarily as cognitive and functional decline, but motor symptoms may also occur, albeit less commonly. Motor symptoms may include gait disturbances, bradykinesia, and muscle rigidity, resembling Parkinson's disease. Non-motor symptoms encompass a wide range of psychiatric and behavioral disturbances, including depression, anxiety, agitation, hallucinations, and sleep disturbances.

AD typically progresses through three main stages: mild, moderate, and severe. In the mild stage, individuals may have difficulty remembering recent events, names, or appointments. As the disease advances to the moderate stage, memory loss becomes more pronounced, and individuals may experience challenges with daily activities such as dressing, bathing, and managing finances. In the severe stage, individuals lose the ability to communicate, recognize loved ones, and perform basic self-care tasks.

The onset of symptoms in AD is insidious, often beginning with subtle cognitive changes that may go unnoticed initially. Memory loss and difficulty with learning new information are early hallmarks of the disease. As AD progresses, symptoms worsen over time, leading to significant functional impairment and dependency on caregivers for assistance with daily activities.

Diagnosing AD involves a comprehensive evaluation, including medical history, physical examination, cognitive assessments, and neuroimaging studies. Magnetic resonance imaging (MRI) and positron emission tomography (PET) scans can visualize brain atrophy and amyloid deposition, aiding in the diagnosis and staging of the disease. Cerebrospinal fluid (CSF) analysis may also be performed to detect biomarkers associated with AD pathology, such as beta-amyloid and tau proteins.

Currently, there is no cure for AD, but several treatment options are available to manage symptoms and slow disease progression. Cholinesterase inhibitors, such as donepezil, rivastigmine, and galantamine, are commonly prescribed to improve cognitive function and manage behavioral symptoms. Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, may also be used to moderate glutamate-mediated excitotoxicity in the brain. Additionally, non-pharmacological interventions, including cognitive stimulation therapy, physical exercise, and caregiver support programs, can help improve quality of life for individuals with AD and their families.

2.4.2. Anti-IgLON5

Anti-IgLON5 disease is a rare neurological disorder characterized by a distinct set of symptoms, often associated with rapid eye movement (REM) sleep behavior disorder. Fenomenologically, patients typically present with a combination of motor and non-motor symptoms. Motor symptoms may include gait instability, dysarthria, and abnormal movements such as chorea or myoclonus. Non-motor symptoms can encompass cognitive

impairment, psychiatric manifestations like hallucinations and paranoia, and sleep disturbances, notably REM sleep behavior disorder.

The etiology of anti-IgLON5 disease remains largely unknown, although it is believed to involve an autoimmune response targeting the IgLON5 protein, a neuronal cell adhesion molecule found in the central nervous system. This autoimmune reaction leads to neuroinflammation and neuronal dysfunction, contributing to the clinical manifestations of the disease.

Symptoms of anti-IgLON5 disease can manifest gradually over months to years, often initially presenting with sleep disturbances and subtle neurological symptoms. As the disease progresses, motor and cognitive symptoms become more pronounced, leading to significant disability and impairment in daily functioning.

Diagnosis of anti-IgLON5 disease relies on a combination of clinical evaluation, neuroimaging studies (such as MRI), polysomnography to assess sleep abnormalities, and the detection of anti-IgLON5 antibodies in the cerebrospinal fluid (CSF) or serum. CSF analysis may reveal oligoclonal bands and elevated protein levels, supporting the diagnosis.

Treatment for anti-IgLON5 disease is primarily supportive and symptomatic, as there is currently no cure for the condition. Management may involve the use of immunomodulatory therapies such as corticosteroids, intravenous immunoglobulin (IVIG), or plasma exchange to suppress the autoimmune response and reduce inflammation. Additionally, symptomatic treatments targeting specific symptoms, such as sleep aids for REM sleep behavior disorder or dopaminergic agents for movement disorders, may be employed to improve quality of life for affected individuals.

2.4.3. SWEDD

SWEDD, or Scans Without Evidence of Dopaminergic Deficit, is a condition characterized by clinical symptoms resembling Parkinson's disease (PD) but without evidence of dopaminergic deficit on imaging studies. Fenomenologically, SWEDD patients may present with both motor and non-motor symptoms typical of PD, including tremor, bradykinesia, rigidity, and postural instability. Non-motor symptoms can include cognitive impairment, autonomic dysfunction, and psychiatric manifestations such as depression and anxiety.

The etiology of SWEDD is not fully understood, but it is believed to encompass a heterogeneous group of conditions that mimic PD clinically but have different underlying pathophysiologies. Possible causes may include other neurodegenerative disorders, drug-induced parkinsonism, or psychogenic movement disorders.

Diagnosis of SWEDD is primarily based on clinical evaluation and neuroimaging studies, particularly dopamine transporter (DAT) imaging using techniques like single-photon emission computed tomography (SPECT) or positron emission tomography (PET). In SWEDD patients, these imaging studies show normal dopaminergic function, distinguishing them from true PD patients.

Treatment of SWEDD is challenging due to the absence of a specific underlying pathology. Management typically involves symptomatic treatment targeting individual symptoms, such as physical therapy for motor symptoms and pharmacotherapy for non-motor symptoms like

depression or anxiety. Additionally, close monitoring and follow-up are essential to reassess the clinical status and adjust treatment as needed.

2.5. Common symptoms

Nothing new will be said in this section, but a list of the most important symptoms, motor and non-motor, discussed so far will be provided for convenience.

2.5.1. Motor symptoms

In idiopathic Parkinson's disease, resting tremor and bradykinesia are more common, while atypical parkinsonian disorders may present with additional symptoms like ataxia and dysarthria. Secondary parkinsonism can be caused by various factors, including medications and other medical conditions, leading to a diverse range of motor symptoms.

Idiopathic Parkinson's Disease:

Resting tremor

Bradykinesia (slowness of movement)

Rigidity

Postural instability

Atypical Parkinsonian Disorders:

Resting tremor

Bradykinesia

Rigidity

Postural instability

Ataxia (loss of coordination)

Dystonia (involuntary muscle contractions)

Dysarthria (difficulty in speech)

Dysphagia (difficulty in swallowing)

Secondary Parkinsonism:

Resting tremor

Bradykinesia

Rigidity

Postural instability

Drug-induced dyskinesia (abnormal involuntary movements)

Gait abnormalities

Akathisia (restlessness)

2.5.2. Non-motor symptoms

Non-motor symptoms in idiopathic Parkinson's disease often include olfactory dysfunction and constipation, while cognitive impairment and autonomic dysfunction are more prevalent in atypical parkinsonian disorders. Secondary parkinsonism can exhibit similar non-motor symptoms to idiopathic Parkinson's disease but may also result from medication side effects, leading to additional non-motor manifestations.

Idiopathic Parkinson's Disease:

Olfactory dysfunction (loss of smell)

Constipation

Depression

REM sleep behavior disorder

Atypical Parkinsonian Disorders:

Cognitive impairment (including dementia)

Psychiatric symptoms (hallucinations, delusions)

Autonomic dysfunction (orthostatic hypotension, urinary problems)

Sleep disturbances (insomnia, excessive daytime sleepiness)

Secondary Parkinsonism:

Cognitive impairment

Psychiatric symptoms

Autonomic dysfunction

Sleep disturbances

Drug-induced symptoms (resulting from medications)

3. Methods

This section presents the methods used to conduct the systematic review. The methodology used in this review follows the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) as a reporting guideline. The remainder of this section describes the Research questions (Section 3.1), the search strategy (Section 3.2), inclusion and exclusion criteria (Section 3.3) and data extraction (Section 3.4). Furthermore, the Diagnostic modes (Section 3.5) and the Technological instrumentation (Section 3.6) were analyzed.

3.1. Research questions

This review aims to collect, process, and anlyse studies in the literature to gather information on differential diagnosis of PD applied to different diagnosis modes, for motor symptoms and non-motor symptoms. To achieve this goal, the following research questions were raised.

RQ-1 Which pathologies are the most critical in the differential diagnosis of PD?

RQ-2 Which technologies and wearable devices have been used in recent studies?

RQ-3 Which diagnostic modes are used and which are the most effective for each type of diagnosis?

RQ-4 What are the challenges and opportunities offered by the development of new and lesser-used diagnostic modes in the differential diagnosis of PD?

3.2. Search strategy

On February 2024, a literature search was conducted on PubMed, IEEE Xplore and ResearchGate databases for all the returned results. The string included keywords related to the diseases under investigation, the sensors and the technology used to collect the data, and the diagnostic modes admitted from the purpose of this work. Specifically, the Boolean search string used was as follows:

(Parkinson) **AND** *(Differential diagnosis)* **AND** *(staging PD OR PD versus OR multisystem atrophy OR progressive supranuclear palsy OR diffuse Lewy body disease OR PD subtype OR PD ON OR PD OFF OR ON-OFF OR idiopathic OR atypical OR secondary pd OR iatrogenic PD OR toxic PD OR metabolic PD OR vascular PD OR tumour PD OR infectious PD OR traumatic PD)* **AND** *(sensor OR wearable OR body-worn OR clothes OR internet of things OR inertial OR IMU OR accelerometer OR gyroscope OR smartphone OR smartwatch OR actigraphy OR force sensor OR insoles OR electromyography OR EMG OR electroencephalography OR EEG OR polysomnography OR PSG OR electrooculogram OR EOG OR electrocardiography OR ECG OR skin conductance OR GSR OR face OR expressions OR hand OR foot OR feet OR Movement OR voice OR sleep OR cognitive OR neuropsychological)*

Some additional filters were applied in the literature search, such as “Free Full Text” (or available for Politecnico di Torino students), “Language: English” and “Only humans (no other animals)”. All retrieved studies were systematically identified and screened, and the data were extracted for relevant information following the PRISMA guidelines (Moher et al., 2015).

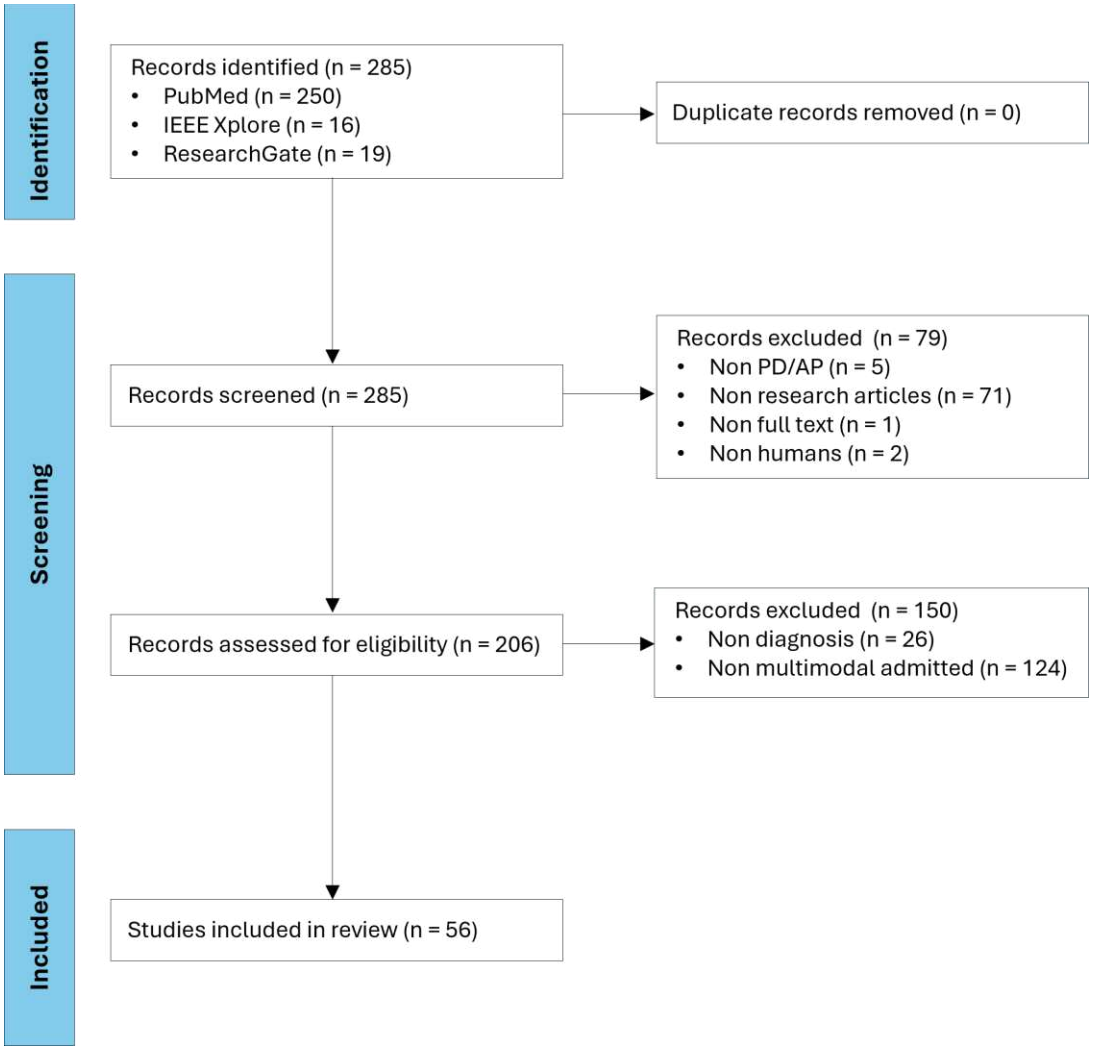

Fig. 1 PRISMA flow diagram of literature search and selection process showing the number of studies identified, screened, and included in the review.

3.3. Inclusion and exclusion criteria

The topic of this review concerns the differential diagnosis of PD, along with some constraints related to the diagnostic modes. In this study, journal articles published between 2016 and February 2024 and written in English were included. The exclusion criteria were as follows:

1. The literature was not written in English.
2. Studies on animals.
3. Papers without peer review, conference papers, books, book chapters, or published as "letter", "comments", "case reports", "survey", "clinical trial", "reviews" or "meta-analysis".
4. Studies involving diagnostic modalities excluded from research: genetic tests, medical imaging, biochemical parameters.
5. Studies that do not deal with diagnosis but with something else, e.g. monitoring, or prediction of response to treatment.

6. Differential diagnoses without at least one idiopathic, atypical or secondary parkinsonism.

3.4. Data extraction

Firstly, candidate studies were selected by reviewing the title and abstract. Then, a more accurate selection, based on a full-text evaluation, was performed for those studies that had passed the first screening phase. Finally, candidate studies that met the eligibility criteria were selected for inclusion in the review. The following information was included in the data extraction procedure:

a. Study identification, including title, authors, publication year and online portal of origin.
b. Type of diagnosis: diseases and symptoms involved.
c. MS or NMS being investigated.
d. Wearable devices and/or sensors used for data acquisition.
e. Diagnosis modes involved in the study and extracted parameters.
f. Information on the statistical approach used to elaborate the collected data.
g. Characteristics of the data set
h. Results

3.5. Diagnostic Modes

In this research study, we wanted to focus on a few specific diagnostic modes, either individually or even together, to check their validity, pros and cons. A brief overview of the methods we chose to consider is therefore presented in the following:

Video Assessment: Video analysis, particularly of the face, hands, and feet, is a valuable tool in the differential diagnosis of Parkinson's disease. Facial expressions in PD patients often become less expressive, a condition known as hypomimia or "masked facies." Clinicians can utilize video recordings to observe the subtleties of facial movements that might not be as apparent during a standard clinical examination. For example, reduced blink rate and diminished emotional expressiveness are common in PD. Similarly, hand and foot movements can be recorded and analyzed for tremors, bradykinesia (slowness of movement), and rigidity. These recordings help in capturing the characteristic rest tremor of PD, which is a key differentiating feature from other types of tremors seen in conditions like essential tremor.

Movement Assessment with Sensors: Movement analysis using sensors provides quantitative data that can enhance the accuracy of PD diagnosis. Inertial sensors placed on different parts of the body can measure movement dynamics such as acceleration, velocity, and angular displacement. These sensors help in objectively assessing gait disturbances, which are prevalent in PD patients. Gait analysis can reveal reduced stride length, increased variability in step timing, and decreased arm swing, which are indicative of PD. Moreover, sensors can be used to evaluate the motor symptoms over time and in different settings, providing a comprehensive picture of the motor impairments associated with the disease. This data can be particularly useful in differentiating PD from other movement disorders like progressive supranuclear palsy or multiple system atrophy, which have distinct gait characteristics.

Voice Evaluation: Voice analysis is another innovative approach in the differential diagnosis of Parkinson's disease. PD often affects the muscles involved in speech, leading to hypophonia (soft speech), monotone voice, and difficulties in articulation. Voice recordings can be analyzed using various acoustic measures to detect these abnormalities. Parameters such as pitch variability, speech rate, and voice quality can be quantified and compared to normative data. Exercises that involve sustained phonation or reading passages aloud can be particularly telling. These voice metrics not only assist in diagnosing PD but also in monitoring disease progression and the effectiveness of treatments.

Cognitive and Neuropsychological Testing: Cognitive and neuropsychological tests are essential in the differential diagnosis of PD, as cognitive impairment is a significant non-motor symptom of the disease. Patients with PD often experience executive dysfunction, visuospatial difficulties, and memory problems. Neuropsychological assessments can include tests such as the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), and specific tasks designed to evaluate executive functions, attention, and working memory. These tests help differentiate PD from other neurodegenerative conditions such as Alzheimer's disease and Lewy body dementia, which have different cognitive profiles.

Electroencephalography (EEG), Electrocardiography (ECG), and Electromyography (EMG): Electrophysiological measures like EEG, ECG, and EMG also contribute to the differential diagnosis of Parkinson's disease. Electroencephalography (EEG) is useful in assessing brain activity and detecting abnormal patterns that may be associated with PD. While EEG changes are not specific to PD, certain patterns, such as a generalized slowing of brain waves, can support the diagnosis when considered alongside other clinical features. Additionally, EEG can help identify comorbid conditions like epilepsy, which may complicate the clinical picture. Electrocardiography (ECG) is employed to evaluate cardiac function, as autonomic dysfunction is common in PD. Patients with PD may exhibit heart rate variability and orthostatic hypotension, which can be detected through ECG. These findings are important in distinguishing PD from other neurodegenerative diseases that do not typically present with significant autonomic involvement. Electromyography (EMG) is primarily used to assess muscle activity and detect abnormalities in motor unit function. In PD, EMG can reveal tremors, bradykinesia, and muscle rigidity. These findings, when combined with clinical assessments, help differentiate PD from other conditions such as essential tremor, which typically lacks the bradykinesia and rigidity seen in PD. EMG can also be useful in ruling out peripheral neuropathies and myopathies, which might mimic some symptoms of PD.

3.6. Technological instrumentation

The differential diagnosis of PD has evolved significantly with the integration of various technological tools. These tools enhance the precision of diagnosis and help differentiate PD from other neurodegenerative disorders. The use of inertial sensors, acoustic sensors, optical sensors, and electrical sensors has become pivotal in modern diagnostic protocols.

Inertial sensors, including accelerometers, gyroscopes, and magnetometers, play a crucial role in monitoring movement. These sensors can be embedded in wearable devices such as wristbands, anklets, or even clothing, allowing continuous and unobtrusive monitoring of a patient's motor activity. Accelerometers measure the acceleration of body parts, which is

particularly useful in detecting tremors. Gyroscopes capture rotational movements, aiding in the assessment of balance and gait. Magnetometers provide directional orientation data, complementing the information gathered by accelerometers and gyroscopes.

Wearable devices equipped with these sensors can record data over extended periods, providing a comprehensive view of the patient's motor function. This long-term monitoring is valuable in capturing the fluctuations in motor symptoms that are characteristic of PD, which might not be evident during a brief clinical examination. Data from these sensors can be analyzed using algorithms to identify patterns and anomalies, contributing to a more accurate diagnosis.

Acoustic sensors, primarily microphones, are used to analyze voice changes, which are common in PD. Patients often experience hypophonia (reduced voice volume), monotonic speech, and dysarthria (slurred speech). Acoustic analysis involves recording the patient's speech and using software to analyze various parameters such as pitch, volume, and speech rate. Changes in these parameters can indicate the presence and progression of PD.

Voice analysis is a non-invasive, cost-effective, and easily repeatable diagnostic tool. It can be conducted remotely, making it accessible to patients who may have difficulty attending frequent clinical appointments. Acoustic sensors provide objective measurements that can be tracked over time, helping to monitor disease progression and response to treatment.

Optical sensors, which use light to detect biological signals, are employed in various diagnostic tools for PD. One common application is in the measurement of blood flow and oxygenation using near-infrared spectroscopy (NIRS). NIRS can be used to assess cerebral hemodynamics, which may be altered in PD. Additionally, optical sensors are used in devices that track eye movements. PD can affect the oculomotor system, leading to abnormalities such as reduced blink rate and impaired saccadic movements. Tracking these eye movements provides valuable diagnostic information.

Furthermore, optical sensors are used in photoplethysmography (PPG) to measure heart rate and other physiological parameters. PPG devices use light to detect blood volume changes in the microvascular bed of tissue. This technology can be integrated into wearable devices to continuously monitor cardiovascular function, which can be affected in PD due to autonomic dysfunction.

Electrical sensors, including those used in electroencephalography (EEG), electrocardiography (ECG), and electromyography (EMG), provide detailed insights into the electrical activity of the brain, heart, and muscles, respectively.

EEG measures the electrical activity of the brain and is particularly useful in identifying non-motor symptoms of PD, such as cognitive impairment and sleep disturbances. PD patients often exhibit specific EEG patterns, such as reduced alpha wave activity and increased theta and delta wave activity. These patterns can help differentiate PD from other conditions like Alzheimer's disease or frontotemporal dementia.

ECG monitors the electrical activity of the heart. PD can affect the autonomic nervous system, leading to cardiovascular abnormalities such as orthostatic hypotension and heart rate variability. Continuous ECG monitoring can detect these abnormalities, providing supplementary data for a comprehensive diagnosis.

EMG assesses the electrical activity produced by skeletal muscles. It is used to evaluate muscle function and detect abnormalities in muscle activation patterns. In PD, EMG can help in the assessment of tremors, rigidity, and bradykinesia. The data obtained from EMG can be used to distinguish between PD and other neuromuscular disorders.

The integration of data from various sensors and technologies into a unified diagnostic framework is the future of PD diagnosis. Advances in machine learning and artificial intelligence (AI) are facilitating this integration by enabling the analysis of large, multidimensional data sets. AI algorithms can identify patterns and correlations that might be missed by human analysis, leading to earlier and more accurate diagnoses.

For instance, combining video analysis with data from inertial sensors can provide a comprehensive assessment of both visible and subtle motor symptoms. Similarly, integrating voice analysis with cognitive test results can enhance the detection of early non-motor symptoms. Moreover, the development of portable and wearable technologies is making these diagnostic tools more accessible. Patients can undergo continuous monitoring in their everyday environments, providing clinicians with real-world data that enhances the understanding of the disease's progression and response to treatment.

4. Results

This section reports the results of the systematic review process. Specifically, Section 4.1 describes the results of the literature search and the selection of studies, while the trend of publication, along with the main application areas, are reported in Section 4.2. Then, in Section 4.3, the differential diagnoses studies screened are analyzed.

4.1. Review workflow

Based on search criteria, 250 papers from PubMed, 16 from IEEE Xplore, and 19 from ResearchGate have been retrieved, for a total of 285 publications. These articles have been screened for titles and abstracts, after which 79 have been excluded, based on the exclusion criteria. The remaining 206 full text articles have been screened for eligibility and 150 records have been excluded according to the exclusion criteria. In the end 56 research studies were included and analyzed. The PRISMA flowchart used for the literature search and selection is shown in Fig. 1.

4.2. Publication trend and objective

Fig. 2 shows the number of publications per year from 2016, together with the macro-categories of membership. The studies collected in this systematic review were organized into five macro-categories of diagnosis: AD vs DLB (21 studies analyzed, 37% of the total), PD vs ET (8 studies, 14%), PD vs PSP vs MSA (14 studies, 25%), PD (9 studies, 17%) and Other diagnoses (4 studies, 7%), Fig. 3.

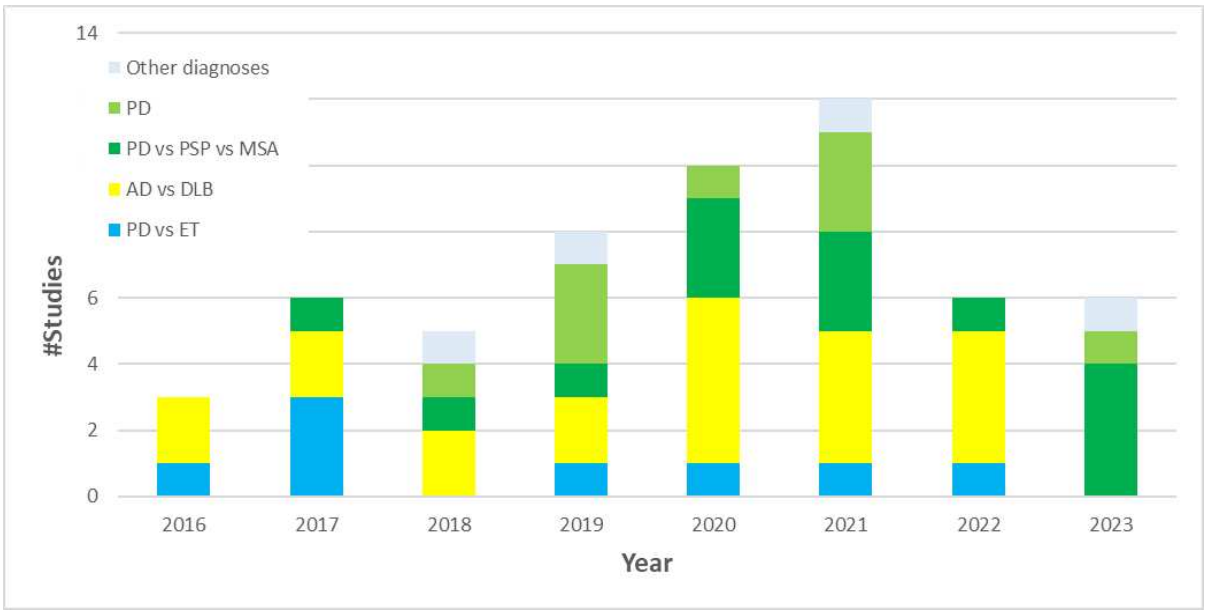

Fig. 2 Number of reviewed articles per year

In this study, a balance was found between motor symptoms (52%) and non-motor symptoms (48%), Fig. 4. Among the various symptoms taken into account, the most frequent were gait impairment in 14% of the total articles (37% of the studies that dealt with this symptom fell under the macrocategory 'PD vs PSP vs MSA'); tremor treated in 23% of the articles (54% of the total cases fell under the category 'PD vs ET'); dementia/MCI was the most treated

symptom in 37% of the studies (with the high probability of 85% falling under the category "AD vs DLB"); voice/speech impairment and dysarthria in 12% of the studies (belonging to "PD vs PSP vs MSA" in 57% of the cases).

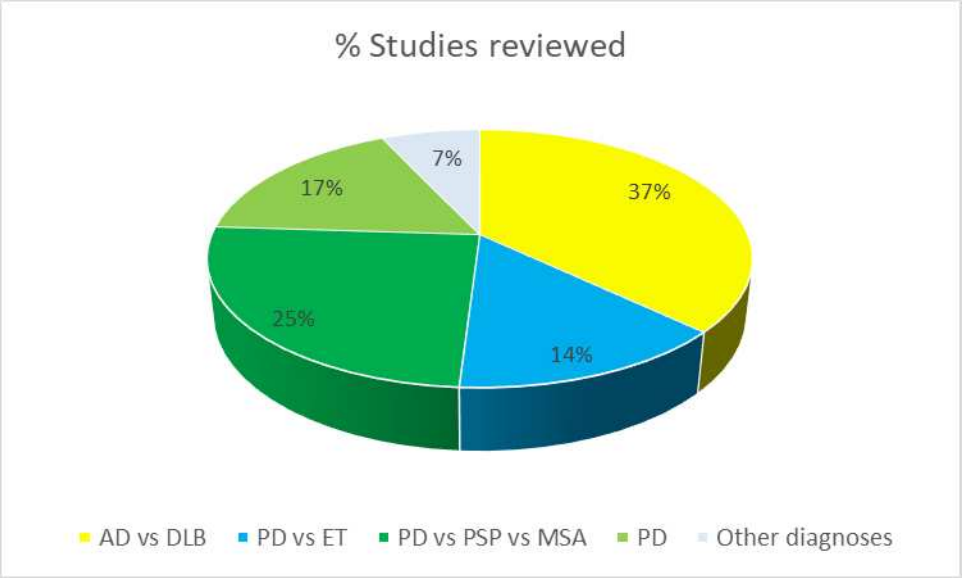

Fig. 3 Percentage of articles collected by category

With regard to the diagnostic modalities used in the study, a balance was found between movement modality and cognitive/neuropsychological/other tests, at 36% each, Fig. 8. While lesser used modalities were video (10%), vocal (9%) and electrophysiological tests (21%). It should be noted that 36% of the studies treated with movement modalities belong to the 'PD vs. ET' category, whereas 70% of the cognitive tests were treated in the 'AD vs. Electrophysiological tests were also widely used in the latter category, in 58% of the cases.

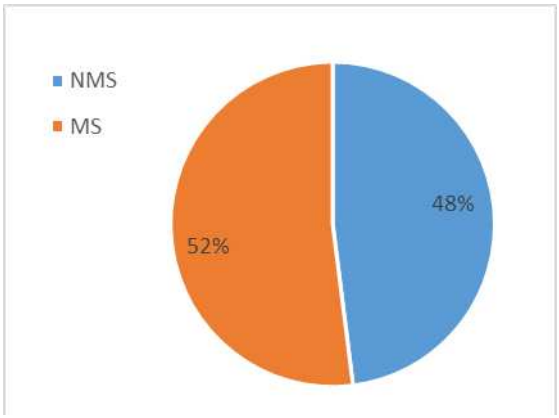

Fig. 4 MS vs NMS in this review

Sensors were used 38 times (Fig. 5 and Fig. 6), predominantly electrical sensors, in 42% of the total cases. Inertial sensors were also very much used, in 31% of the total cases of sensors used; 50% of the cases in which these sensors were used belong to the 'PD vs. ET' category. By contrast, acoustic sensors, especially microphones, were used less, in 10% of the cases (50% of the cases in which they were used belonged to 'PD vs PSP vs MSA') and optical sensors, in 16% of the cases. Wearable devices were also used in 27% of the total studies, especially in 'PD vs ET' (40% of wearable device cases), Fig. 7. Finally, for data analysis and processing, 41% of the studies made use of ML algorithms.

4.3. Differential diagnoses analyzed

In this section, a short overview of the diagnoses considered in the study is given, while in the following chapters they will be analyzed more in detail.

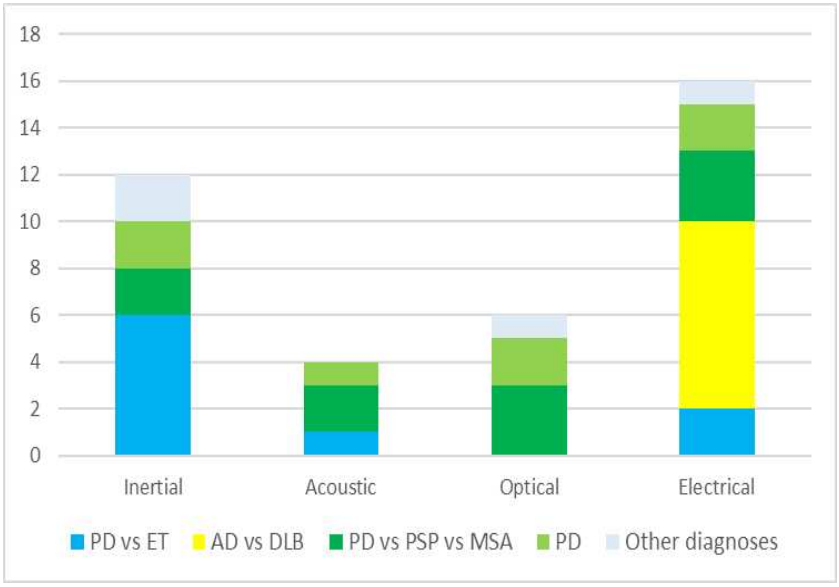

Fig. 5 Number of sensors used in the review

Although not uniquely defined and classifiable differential diagnoses were found, it was nevertheless possible to fall back on five macro-categories of multimodal differential diagnoses:

- *AD vs DLB*: Alzheimer's disease (AD) and Dementia with Lewy Bodies (DLB) are two of the most common forms of dementia, and while they have distinct pathologies, they share several similarities that can complicate diagnosis and treatment. Understanding these similarities, the common symptoms, and the challenges in differential diagnosis is crucial for effective patient care.
  Both AD and DLB are neurodegenerative disorders that primarily affect older adults, leading to progressive cognitive decline. Patients with either condition often experience memory loss, confusion, and difficulties with executive functions such as problem-solving and planning. Additionally, both diseases can result in changes in mood and behavior, including depression, apathy, and anxiety
- *PD vs ET*: Parkinson's Disease (PD) and Essential Tremor (ET) are two neurological conditions that share certain features, which can complicate their diagnosis and treatment. Both disorders involve tremors, but they differ significantly in their pathophysiology, progression, and treatment. Understanding these similarities, the common symptoms, and the challenges in differential diagnosis is crucial for proper patient management.
  Both PD and ET are movement disorders that manifest with tremors, which is a primary reason they are often confused. Tremors in both conditions can significantly impact a patient's quality of life, leading to difficulties in performing daily activities. Additionally, both conditions can present in a similar age group, typically affecting older adults, though ET can also begin earlier in life. There is also some genetic overlap, as family history can be a factor in both PD and ET.

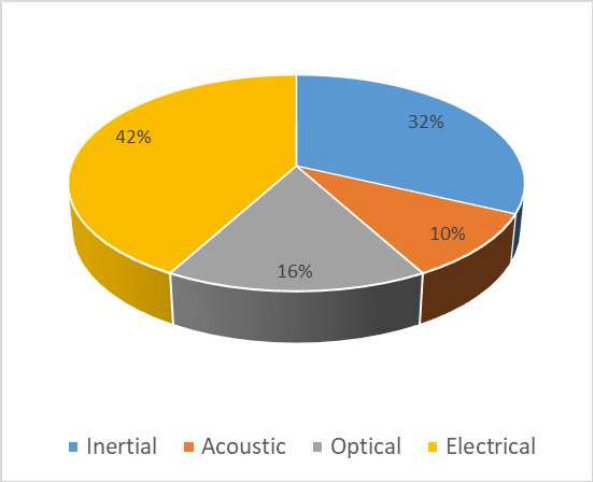

Fig. 6 Percentage of sensor types used

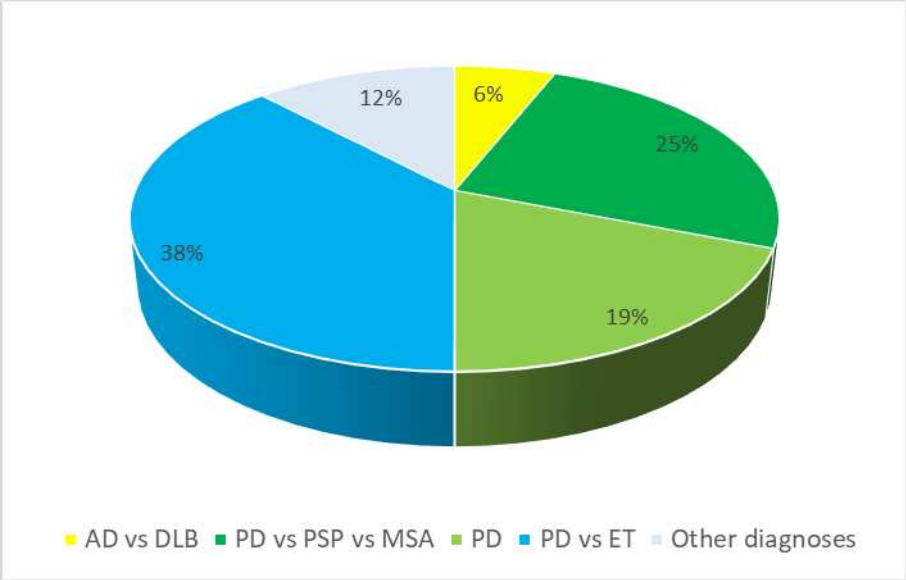

Fig. 7 Percentage of wearable devices used per category

- *PD vs PSP vs MSA*: Parkinson's Disease (PD), Progressive Supranuclear Palsy (PSP), and Multiple System Atrophy (MSA) are neurodegenerative disorders that share many clinical features, making their differential diagnosis particularly challenging. Understanding the similarities, common symptoms, and diagnostic complexities of these conditions is essential for accurate diagnosis and appropriate treatment. All three conditions—PD, PSP, and MSA—fall under the umbrella of parkinsonian syndromes, which are characterized by similar motor symptoms. These include bradykinesia (slowness of movement), rigidity, and postural instability. Tremors are also a common feature, particularly in PD and MSA, although they may be less prominent in PSP. Additionally, these disorders typically affect individuals in middle to late adulthood and have a progressive nature, leading to increasing disability over time.
- *PD*: This chapter will explore the current state of PD diagnosis, highlighting recent technological advancements and their implications for future applications in differential diagnosis. By understanding and leveraging these innovations, clinicians can improve the accuracy of PD diagnosis, potentially leading to better patient outcomes and more targeted therapies.
- *Other diagnoses*: The diagnoses in this section are only four. They were not classifiable for any of the previous sections but are nevertheless included in the collection of this systematic review work, due to the presence of idiopathic PD, atypical parkinsonisms or

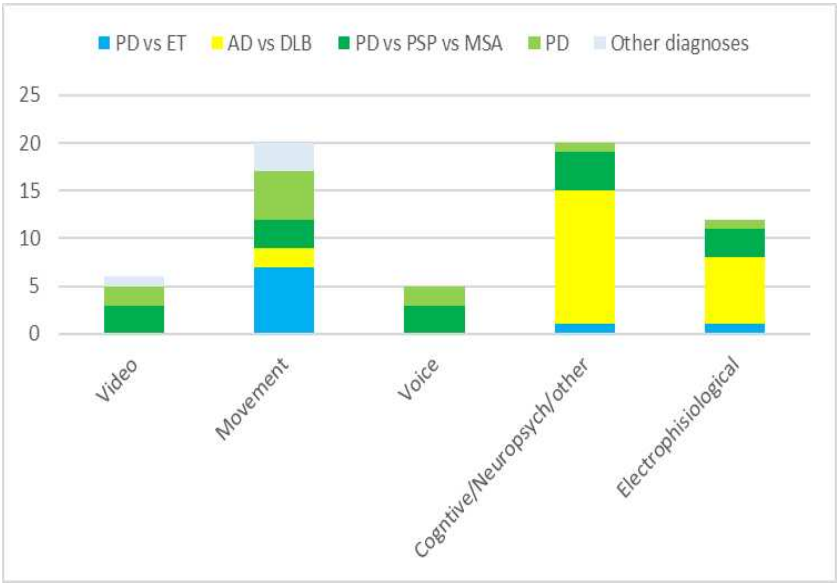

Fig. 8 Diagnostic modalities involved per category

secondary parkinsonisms: PD (vs ALS vs HD), PD vs SWEDD (Scans Without Evidence of Dopaminergic Deficit), PD vs VaP (Vascular Parkinsonism) and PSP vs anti-IgLON5.

In the following, everyone of these categories will be taken into account in detail, specifying for each of them: the diseases involved, the patient datasets, the symptoms and the various diagnostic modalities used, reporting data and numerical results.

4.3.1. AD vs DLB

Data source and sample size:

The research studies analyzed used only private data sets, mainly from public hospitals, private clinics specializing in the treatment of the disorders in question and universities. 21 studies were here analyzed.

The number of patients enrolled in the various studies ranges from a minimum of 39 to a maximum of 3093 (mean: 396.57, median: 110). In general, most of the studies (90%) involved fewer than 400 patients, with only 2 studies (10%) involving more than 1000 patients.

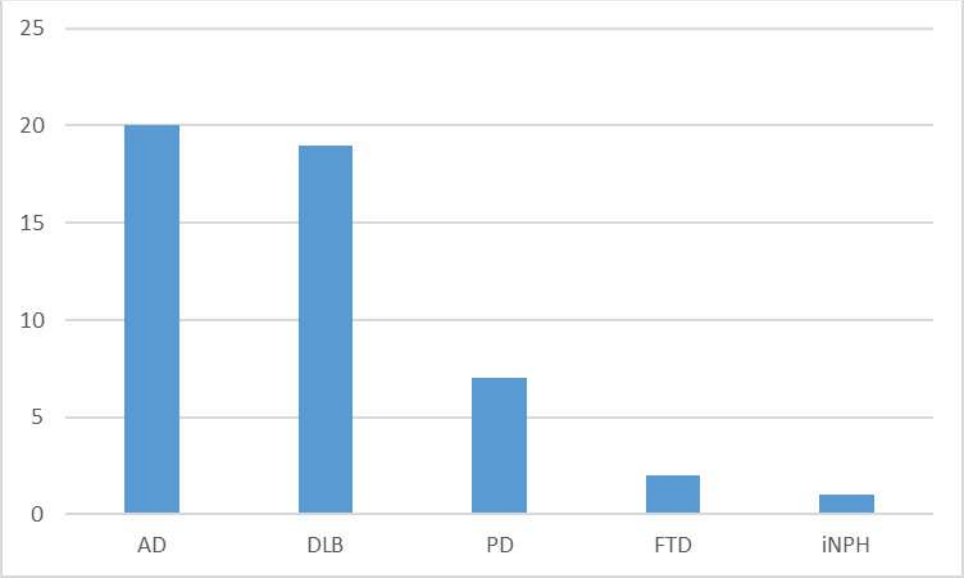

Fig. 9 Number of diseases treated in this section

The diagnoses studied focused predominantly on the analysis of AD (95%) and DLB (90%), with fewer cases also involving PD, FTD and iNPH. Fig. 9 shows the range of cases in which all the diseases in the current section were observed. The most treated diagnoses were 'AD vs DLB' (62%) and 'AD vs DLB vs PD' (19%), Fig. 10.

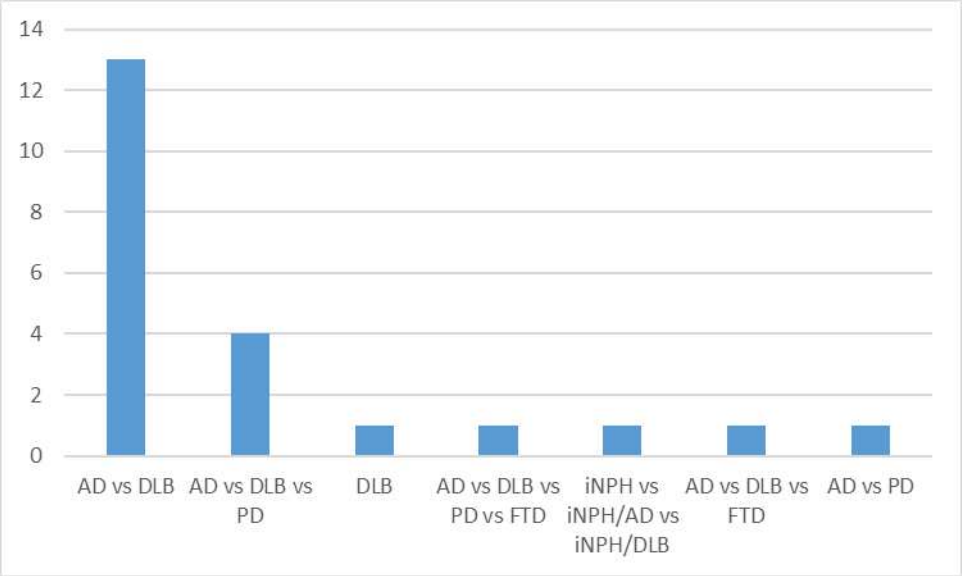

Fig. 10 Number of diagnoses analyzed in "AD vs DLB"

Symptoms:

Both AD and DLB, the main diseases discussed in this section, are two disorders that predominantly involve dementia, impaired cognitive functions and memory disorders. It is therefore not surprising that the majority of symptoms detected in the various studies are NMS in nature (90%), compared to a very low number of cases in which MS is involved (10%). In particular, the most frequently treated symptoms are dementia (52%) and MCI (43%), Fig. 11.

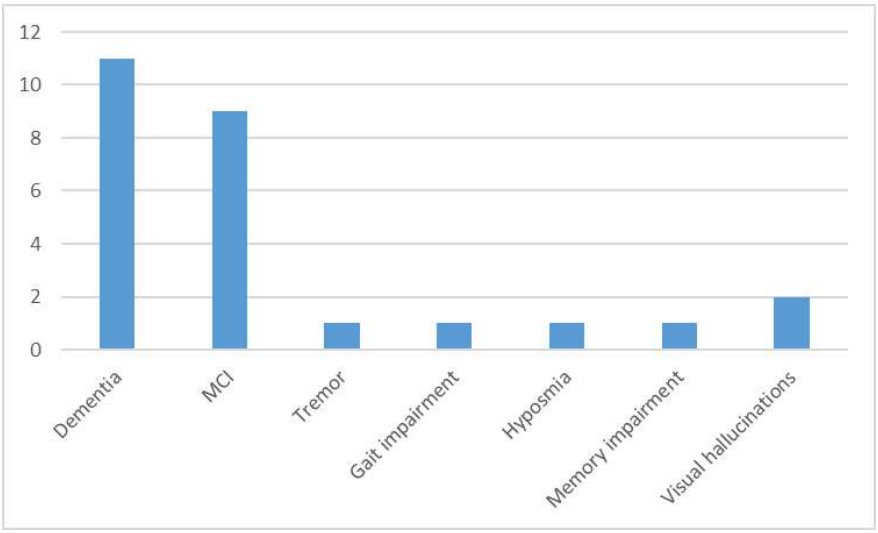

Fig. 11 Symptoms per "AD vs DLB" articles

Multimodal and instrumentation:

With regard to the diagnostic modalities used, given the cognitive nature of the main disorders treated here, it is not surprising that the majority of studies (57%) focused on analyses of cognitive tests such as the Mini-Mental State Examination (MMSE), the Addenbrooke's Cognitive Examination III (ACE-III), the Addenbrooke's Cognitive Examination-Revised (ACE-R) and the Montreal Cognitive Assessment (MoCA), (Mc Ardle et al., 2019; Prats-Sedano et al., 2020; Ala et al., 2022; Yamamoto et al., 2017; Kozlova et al., 2021; Schumacher et al., 2020). MMSE is a commonly used 30-point questionnaire designed to assess general cognitive functioning. It is widely used to detect cognitive impairment and conditions like dementia, evaluating areas such as orientation, attention, memory, language, and visuospatial skills. ACE is a more comprehensive cognitive test than the MMSE, covering a broader range of

cognitive domains including attention, memory, verbal fluency, language, and visuospatial abilities. It is particularly useful for differentiating between different types of dementia. Finally, MoCA is another cognitive screening tool that detects mild cognitive impairment. It assesses a wide array of cognitive functions such as attention, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. The MoCA is favored for its extensive coverage of cognitive domains, making it more comprehensive than the MMSE.

Other tests were occasionally used, such as the Hopkins Verbal learning test and the Category Fluency CFL (Azar et al., 2020), Lewy Body Dementia Module LBD-MOD (Galvin et al., 2021), Fall Risk Index-21 FRI-21 (Tsujimoto et al., 2022), UPSIT test (University of Pennsylvania Smell Identification Test) (Beach et al., 2020),Clinician Assessment of Fluctuation CAF (Van Dyk et al., 2016),Pareidolia test (Mamiya et al., 2016), Lewy Body Composite Risk Score LBCRS and Assessment Toolkit for DLB AT-DLB (Russo et al., 2022), RAVLT test, Grooved Pegboard test and Stroop tests (Kamohara et al., 2020). The Hopkins Verbal Learning Test is a neuropsychological assessment that evaluates verbal learning and memory by asking participants to recall a list of words. The Category Fluency Test (CFL) measures verbal fluency by requiring individuals to generate words belonging to specific categories within a limited time. The Lewy Body Dementia Module is a diagnostic tool designed to assess symptoms specific to Lewy Body Dementia (LBD), aiding in the identification of this condition. The Fall Risk Index-21 assesses an individual's risk of falling, considering various factors to predict and prevent falls. The University of Pennsylvania Smell Identification Test (UPSIT) evaluates olfactory function and is often used to detect conditions like Parkinson's disease and LBD, which commonly affect the sense of smell. The Clinician Assessment of Fluctuation (CAF) measures fluctuations in cognitive function, particularly relevant in diagnosing LBD. The Pareidolia Test examines the tendency to perceive meaningful images in random patterns, which can be indicative of certain neuropsychiatric conditions. The Lewy Body Composite Risk Score is a tool used to estimate the likelihood of having LBD based on various clinical symptoms. The assessment toolkit for Dementia with Lewy Bodies (DLB) includes a comprehensive set of evaluations tailored to diagnose DLB accurately. The Rey Auditory Verbal Learning Test (RAVLT) assesses auditory verbal memory by presenting a list of words and testing recall and recognition. The Grooved Pegboard Test measures fine motor skills and manual dexterity, often used in neurological assessments. Finally, the Stroop Tests evaluate cognitive flexibility and attention by requiring individuals to name the color of the ink used to print words, which can be congruent or incongruent with the word's meaning, highlighting the ability to manage cognitive interference.

Finally, a second widely used diagnostic modality was electrophysiological tests, in terms of both EEG/quantitative-EEG (28%) (Suzuki et al., 2022; Mehraram et al., 2020; Peraza et al., 2018; Stylianou et al., 2018; Garn et al., 2017; Schumacher et al., 2020) and Transcranial Magnetic Stimulation, just one case (Padovani et al., 2019). EEG and qEEG are both techniques used to measure and analyze the electrical activity of the brain, but they differ in data processing and analysis. EEG records brain wave patterns using electrodes on the scalp and is used to diagnose conditions like epilepsy and sleep disorders by providing raw data in wave patterns. qEEG goes further by applying complex mathematical algorithms to the raw EEG data, creating detailed maps of brain activity, which can identify specific patterns and abnormalities not visible in standard EEG, useful for detailed assessments like cognitive

evaluations and neuropsychiatric research. While TMS is another diagnostic and therapeutic technique that involves using a rapidly changing magnetic field to influence the electrical activity in the brain. TMS generates a magnetic field that induces electric currents in specific regions of the brain, which can help activate or modulate cortical motor areas and the corticospinal tract without invasive procedures. It is used both for treatment, such as in depression, and for diagnostic purposes to understand brain function and connectivity.

Only 9% of the diagnoses used a movement modal technique, focusing on the process of handwriting (Yamada et al., 2022) and on gait impairment (Mc Ardle et al., 2019), this last one have been combined to MMSE and ACE-III cognitive tests.

As this is a diagnostic section that mainly involves cognitive tests and questionnaires, the technological instrumentation employed is quite meagre. That said, however, all studies that have employed electrophysiological examinations (Suzuki et al., 2022; Mehraram et al., 2020; Peraza et al., 2018; Stylianou et al., 2018; Garn et al., 2017; Schumacher et al., 2020; Padovani et al., 2019) have made heavy use of electrical sensors in the form of electrodes. In addition, one study (Yamada et al., 2022) made use of digitizing tablet and pen (Wacom Cintiq Pro 16; sampling rate: 180 Hz; pen pressure levels: 8,192; pen inclination resolution: 1 degree; screen size: 345 × 194 mm (2560 × 1440 pixels)), while another study (Mc Ardle et al., 2019) analyzed gait impairment using a 7 meter × 0.6 meter (length × width) instrumented walkway (GAITRite, version 4.5; CIR Systems Inc., USA), as shown in Fig. 12.

Fig. 12 GAITRite, version 4.5; CIR Systems Inc., USA

Results:

As mentioned earlier, twelve studies followed a cognitive/neuropsychological approach, two of which (Mc Ardle et al., 2019; Schumacher et al., 2020) were carried out as support for diagnostic modalities of movement and an electrophysiological test respectively.

In Azar et al. (2020), neuropsychological measures ,included memory recall and recognition total (Hopkins Verbal learning test), naming (i.e., Boston naming test), verbal fluency (Category fluency, CFL), processing speed (Trail Making Part A, TMT-A), executive functioning (Trail Making Part B, TMT-B), and pentagon copy from the (modified Mini-Mental State Exam (mMMSE), found differences in phonemic fluency, processing speed, and visuoconstruction between AD and AD + LBD. Despite limitations like small sample sizes, these findings highlight the need for further research to improve diagnostic accuracy and treatment differentiation, with excellent sensitivity values for the verbal fluency and processing speed tests (96.4% and 92.9% respectively) and moderately high specificity and sensitivity values for the pentagon copy (spec: 72.7%, sens:75%). Table 1 (Appendix A) shows the results from the studies of this section. In Galvin et al. (2021) the DLB module (LBD-MOD) is proposed as diagnostic method, that provided excellent characterization of core and supportive features to differentiate DLB from AD and healthy controls while also

characterizing features of MCI-DLB, with a p-value<.001 that indicates a significant difference in bradykinesia, rigidity, postural instability, and resting tremor scores in DLB patients compared to AD patients. In Mc Ardle et al. (2019) MMSE and ACE-III cognitive tests have been used as support to an instrumented walkway (GAITRite, version 4.5; CIR Systems Inc., USA) to evaluate the gait impairment in DLB and AD patients, with low specificity (40%) and modest sensitivity (73%). Gait differences in LBD and AD highlight executive function's role in gait variability. Gait reflects neuropathological changes linked to motor and cognitive pathways, suggesting it as a proxy for underlying neurodegenerative pathology. Asymmetric gait in LBD underscores diverse pathological origins. In Tsujimoto et al. (2022) the Fall Risk Index-21 (FRI-21) module, composed by 21 items, including previously established risk factors for falls, such as the physical function, presence of geriatric syndromes, and environmental factors, have been used. It reveals increased fall risk and frailty in DLB (spec: 84%; sens: 56%), particularly in younger patients with mild cognitive decline. Despite cognitive dysfunction limitations, the study supports tailored interventions. In Prats-Sedano et al. (2020) diagnosis was carried out using the Addenbrooke's Cognitive Examination-Revised (ACE-R). The study confirms ACE-R's effectiveness and robustness in diagnosing dementia(spec: 88%; sens: 96%), distinguishing DLB from AD (spec: 68%; sens: 82%), and detecting cognitive impairment patterns. ACE-R shows good sensitivity but limited negative predictive value. Clinical implications include better treatment, reduced hospitalizations, and enhanced participation in clinical trials. In Ala et al. (2022) distinct cognitive differences between AD and DLB were demonstrated using MMSE-based equations with a high PPV but low sensitivity. It highlights clinical utility in real-world settings, but notes limitations such as inconsistent administration of the MMSE and small sample size. Future research should include biomarker additions and autopsy confirmations. The study of Yamamoto et al. (2017) shows that updated diagnostic criteria improve DLB recognition. MoCA scores and clock drawing tests effectively differentiate DLB from Alzheimer's Disease. Key DLB indicators include visual hallucinations and visuospatial impairment. Neuroimaging is useful but costly. Limitations are retrospective design and unmatched AD and DLB groups. In Van Dyk et al. (2016) they validated the Clinical Assessment of Fluctuation (CAF) scale's reliability for assessing fluctuating cognition in dementia, especially DLB, with high interrater reliability and effective differentiation from probable AD. Limitations included a small sample size and potential biases, indicating the need for further research, despite high specificity (95.5%) and moderate sensitivity (63.5%). The study of Russo et al. (2022) showed a 26% prevalence of DLB diagnosis, higher than autopsy-proven rates. It found good questionnaire agreement and effective toolkits for diagnosing probable DLB, emphasizing cognitive fluctuations and visual hallucinations. Limitations included missing comorbidity data and biomarker validation, highlighting the need for standardized symptom assessment. In Kamohara et al. (2020) neuropsychological tests effectively diagnose iNPH, differentiating it from AD and PD comorbidities. Key tests—RAVLT, Grooved Pegboard, Stroop colour-naming, and interference tests—show significant differences between groups. Serebrospinal fluid shunting improves cognitive deficits, especially in iNPH with AD comorbidity. Standardized protocols are essential for consistent diagnosis. In Schumacher et al. (2020) they compared EEG measures in MCI-AD, MCI-LB, and controls, finding more severe abnormalities in MCI-LB linked to Lewy bodies. Diagnostic accuracy for MCI-LB versus MCI-AD was moderate, with MCI-LB showing EEG slowing and increased pre-alpha power. High specificity but low sensitivity complicates differentiation. Then in Kozlova et al. (2021) temporary memory binding (TMB) impairment

specific to AD was found, with no significant impairment in PD-D patients. ROC analyses confirmed the efficacy of the TMB task in distinguishing AD from controls and PD. The robustness of the study is highlighted by the consideration of the cognitive continuum of PD and the demonstration of the clinical utility of the TMB for differential diagnosis. Two tests were then carried out concerning symptoms such as visual hallucinations (Mamiya et al., 2016) and hyposmia (Beach et al., 2020). The first one was based on the combined pareidolia test, which effectively correlates with visual hallucinations and distinguishes between DLB and AD with high sensitivity and specificity. The scene test differentiates DLB from AD but poorly correlates with hallucinations, while the noise test correlates with hallucinations but is less effective in differentiation. While the second one showed that α-synuclein pathology impacts olfaction, aiding differentiation between AD and DLB. DLB exhibits more pronounced pathology in the frontal cortex and amygdala, influencing olfactory dysfunction. Olfactory function tests are promising. In both cases, better diagnostic methods are needed.

The study of Yamada et al. (2022) was then based on the analysis of handwriting with ML classification models as a mode of differential diagnosis between AD and DLB, showing that drawing analysis as a promising tool for distinguishing AD and DLB, with a high accuracy in distinguishing DLB from Healthy Controls (85.3%). It emphasizes developing user-friendly diagnostic tools and highlights drawing features as potential markers for accurate diagnosis. Further research is needed to validate findings and explore additional diagnostic markers.

Finally, several case studies using electrophysiological examinations as a diagnostic modality were analysed: mainly EEG but also a case of Transcranial Magnetic Stimulation (Padovani et al., 2019). In Suzuki et al. (2022) they validated an EEG-derived machine learning algorithm for distinguishing DLB from AD, achieving 79.5% accuracy, 72.2% sensitivity, and 85.7% specificity. Excluding certain patients improved sensitivity and specificity. Limitations include small sample size and lack of neuropathological confirmation. In Mehraram et al. (2020) they showed reduced EEG connectivity in dementia, especially in the α band. Significant differences between DLB and AD were noted in the β band. Despite limitations, the findings support EEG's diagnostic value for dementia and highlight the need for further research on network alterations. The study of Peraza et al. (2018) found significant EEG measure differences between dementia patients and healthy controls. Key measures, including dominant frequency and phase lag index, effectively differentiated between AD and DLB, showing high diagnostic potential and moderate/high values of specificity and sensitivity in distinguishing AD vs DLB (85%, 80% respectively). Limitations included medication effects and the need for longitudinal assessments. In Stylianou et al. (2018) they found that EEG measures can effectively differentiate between AD and DLB, with AD patients showing higher theta-alpha dominant frequency variability (DFV). DLB patients had a positive correlation between DFV and cognitive fluctuations. QEEG variables showed high accuracy in distinguishing DLB from AD, indicating robust diagnostic potential (spec: 83.3%; sens: 92.3%). In Garn et al. (2017) extensive signal processing was used and 100% accuracy in differential diagnosis among dementia types using QEEG features and SVM classifiers was achieved. Its robust methodology and cost-effectiveness make QEEG a promising tool, though larger studies are needed for validation. Finally, in Padovani et al. (2019) they showed that TMS markers enhance diagnostic confidence in MCI patients similarly to amyloid markers. TMS is non-invasive, cost-effective, and useful for early diagnosis. Combining TMS with other markers improves accuracy, but further validation through longitudinal and real-world studies is needed.

4.3.2. PD vs ET

Data source and sample size:

The research studies analyzed used only private data sets, mainly from public hospitals, private clinics and universities.

In this section 8 articles were analyzed. The number of patients enrolled in the various studies ranges from a minimum of 27 to a maximum of 712 (mean: 134.12, median: 52). In general, most of the studies (87.5%) involved fewer than 100 patients, with only one study (12.5%) involving more than 100 patients.

The diagnoses studied focused only on differentiating PD vs ET.

Symptoms:

Both PD and ET, the main diseases discussed in this section, are two disorders that predominantly involve movement impairment. It is therefore not surprising that the majority of symptoms detected in the various studies are MS (87.5%), compared just one case in which NMS is involved (12.5%), Fig. 13. In particular, the most frequently treated symptom is tremor (87.5%), while only on study treated depressive symptoms (12.5%).

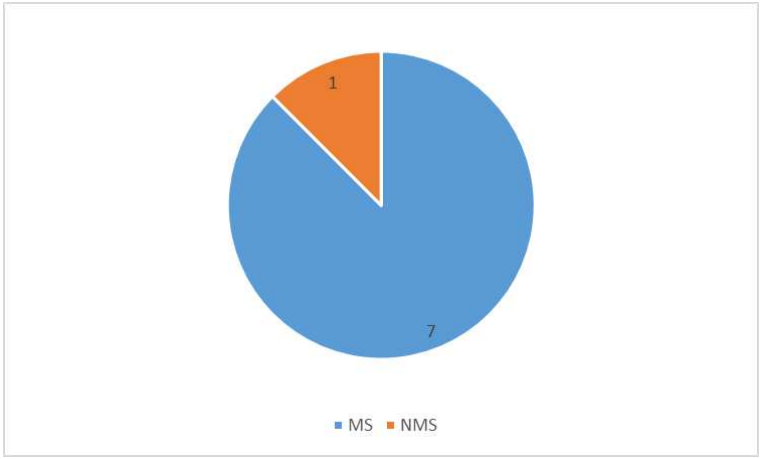

Fig. 13 MS vs NMS in "PD vs ET" section

Multimodal and instrumentation:

Given the frequency of motor symptoms in the study of the differential diagnosis between PD and ET, most studies (87.5%) examined movement tests, analyzing hand tremor and tremor in general, making extensive use of technological instrumentation: inertial sensors have been used in 75% of the studies, while electrical sensors in 25%. Furthermore, wearable devices were used in 75% of the studies. In particular, in Shahtalebi et al. (2021) an inline 3D accelerometer (#317A Noraxon U.S.A. Inc.) was used on the hand dorsum, capturing tremor data in real-time with the TeleMyoTM G2 system at 1500 Hz, transmitting to MyoResearch XP software, while in Sushkova et al. (2020) EMG electrodes were placed on wrist and ankle extensor muscles, and accelerometer sensors on the back of the hands: recordings were made with arms straightened on armrests and with arms outstretched forward. Then, the study of Yang et al. (2019) used an iPad and Apple Pencil to digitize hand-drawing patterns, recording handwriting trajectories with digital sensors. Tremor levels were assessed using frequency spectrum analysis, drawing velocity, and polar expression features. Machine learning methods, including SVM and neural networks, were employed for automated tremor classification. In Barrantes et al. (2017) smartphone's built-in triaxial accelerometers (iPhone 5S, Apple Inc, USA) recorded tremor data from patients' hands, processed with SensorLog software, and sent online for analysis. This method uses frequency spectrum analysis to differentiate Parkinson's disease from essential tremor under routine clinical conditions. In di

Biase et al. (2017) tremor data were collected using triaxial accelerometers and a velocity-transducing laser. Devices used included Opal sensors (APDM, Inc), Brainvision acceleration sensors, and various accelerometers from Biometrics Ltd and Twente Medical Systems International. Data were processed in Matlab, utilizing filtering, principal component analysis, and Hilbert envelope methods to analyze tremor characteristics. In Locatelli et al. (2017) the MuSe platform was used, a miniaturized multi-sensor wearable device integrating a 32-bit microcontroller, 3D geomagnetic System-in-Package, high-capacity serial NOR Flash memory, and Bluetooth module. It features multiple high-performance sensors for accelerometer and gyroscope data, supporting real-time data streaming and logging up to 200 Hz. Then, in Surangsrirat et al. (2016) they used a 6-DOF IMU measuring tri-axial acceleration and angular velocity at 125 samples/sec is used. Attached to the wrist and middle finger, it records data during kinetic (nose-target hand movement) and resting tasks. Signals are wirelessly transmitted to a PC for analysis. Finally, one study (Ratajska et al., 2022) differs from all others, carrying out the differential diagnosis not by means of movement modalities but by cognitive tests, based on depressive symptoms, apathy and anxiety. Mood measures included the Beck Depression Inventory-II, Apathy Scale, and State-Trait Anxiety Inventory. Cognitive assessments involved the Dementia Rating Scale-2 or Montreal Cognitive Assessment, followed by tests on memory, executive function, and attention/working memory. Motor severity was evaluated using the Fahn-Tolosa-Marin Clinical Rating Scale and Unified Parkinson's Disease Rating Scale.

Results:

As seen in the preceding paragraphs, most of the studies concerning the differential diagnosis of PD vs. ET were carried out predominantly with movement-related diagnostic methods, given the motor nature of the symptoms common to the two disorders under consideration, while only in one case was a different method used. Below are the results of the studies analysed.

The study of Ratajska et al. (2022) found similar mood scores in PD and ET, higher than controls, with only PD showing significantly higher apathy. Both groups had lower cognitive performance than controls. Limitations include cross-sectional design, self-reported measures, and a narrow focus on mood's effect on cognition. In Shahtalebi et al. (2021) the study emphasizes NeurDNet's use of deep learning for improved generalization and explainable AI for insights. It highlights the framework's large dataset, sequential processing, and cost-effective accelerometers, demonstrating superior accuracy (NeurDNet reports a maximum accuracy of 95.55% when the training/test ratio is 3:1, with 75% of the data reserved for training) and robustness compared to previous methods, showcasing its clinical viability. Then in Sushkova et al. (2020) they showed that combining wave trains from various sources improves early and differential diagnosis of PD and ET. Using genetic algorithms and bootstrap methods, it enhances diagnostic robustness and independence from device characteristics, promising a specific diagnostic method based on muscle activity analysis. The accuracy of early-stage PD recognition is reported as about 100%, while the accuracy for differential diagnosis (PD vs ET) is about 90%. In Yang et al. (2019) the study's method using hash transformation and a GRNN-based classifier significantly improved the accuracy of screening PD and ET symptoms from 88.27% to 98.93%. This non-invasive approach is effective for preliminary diagnoses and at-home monitoring, with benefits in easy pattern acquisition and implementation using portable devices. Barrantes et al. (2017) proposed a

study showing smartphone accelerometers effectively differentiate PD from ET, providing a feasible and accessible diagnostic tool for clinical settings. It highlighted potential improvements with larger cohorts and machine learning, recommending further validation in broader populations and multicenter studies for robust results. The study of di Biase et al. (2017) found that Tremor Stability Index (TSI) is a robust, non-invasive measure for accurately distinguishing PD tremor from ET, validated across diverse datasets with ~90% accuracy. It is consistent across devices and demographics, offering a reliable diagnostic tool superior to costly radionucleotide studies. Finally, in Locatelli et al. (2017) the study's wearable device effectively differentiated PD tremors from ET in 27 subjects, showing distinct tremor patterns in resting vs. active tasks. Graphical analysis indicated potential for automated classification using machine learning, with future efforts focusing on hardware improvement and sample size expansion. While, in Surangsrirat et al. (2016) temporal fluctuation analysis using angular velocity sensors effectively distinguished PD from ET, demonstrating high diagnostic accuracy. Future studies will expand to include more participants and explore additional sensor modalities for enhanced diagnostic capabilities.

4.3.3. PD vs PSP vs MSA

Data source and sample size:

The research studies analyzed used only private data sets, mainly from public hospitals, private clinics specializing in the treatment of the disorders in question and universities. 14 studies have been analyzed.

The number of patients enrolled in the various studies ranges from a minimum of 22 to a maximum of 774 (mean: 156, median: 104). In general, most of the studies (69%) involved fewer than 120 patients, with only 23% of the studies involving more than 200 patients.

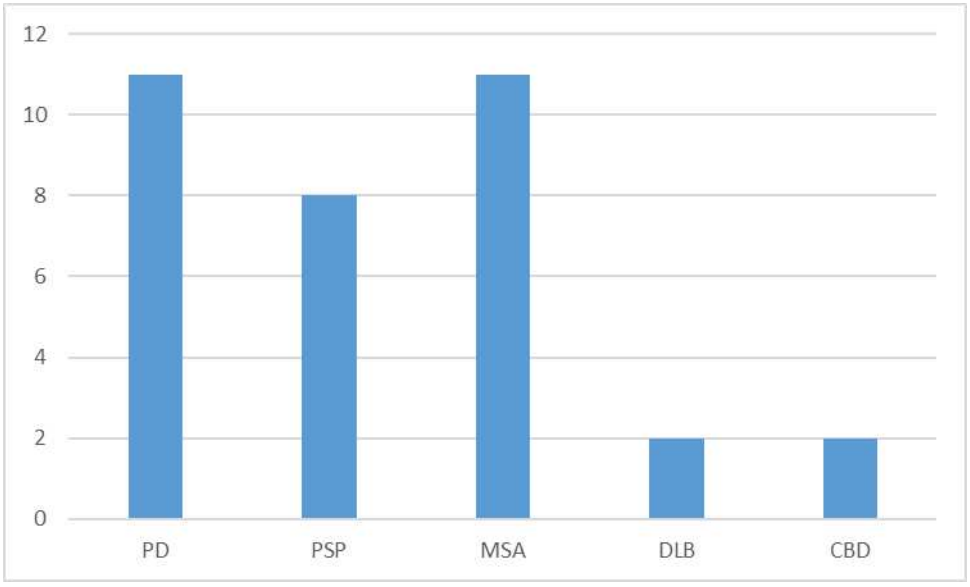

Fig. 14 Diseases treated in "PD vs PSP vs MSA"

The diagnoses studied focused predominantly on the analysis of PD and MSA (78%) and PSP (57%), with fewer cases also involving DLB and CBS. Fig. 14 shows the range of cases in which all the diseases in the current section were observed. The most treated diagnosis was 'MSA vs PD' (43%), Fig. 15.

Symptoms:

Both PD and MSA, the main diseases discussed in this section, are two disorders that involve both motor symptoms (57%), such as gait impairment (21%) (Schröter et al., 2023; Wu et al., 2022; Amboni et al., 2021) and dysarthria (21%) (Das et al., 2019; Li et al., 2018; Kowalska-Taczanowska et al., 2020), and non-motor symptoms (43%), such as hyposmia (14%) (El Otmani et al., 2023; Shill et al., 2021), urinary disfunction (14%) (Hu et al., 2023; Yamamoto et al., 2017), oropharyngeal disfunction (14%) (Gandor et al., 2020), etc. Fig. 16.

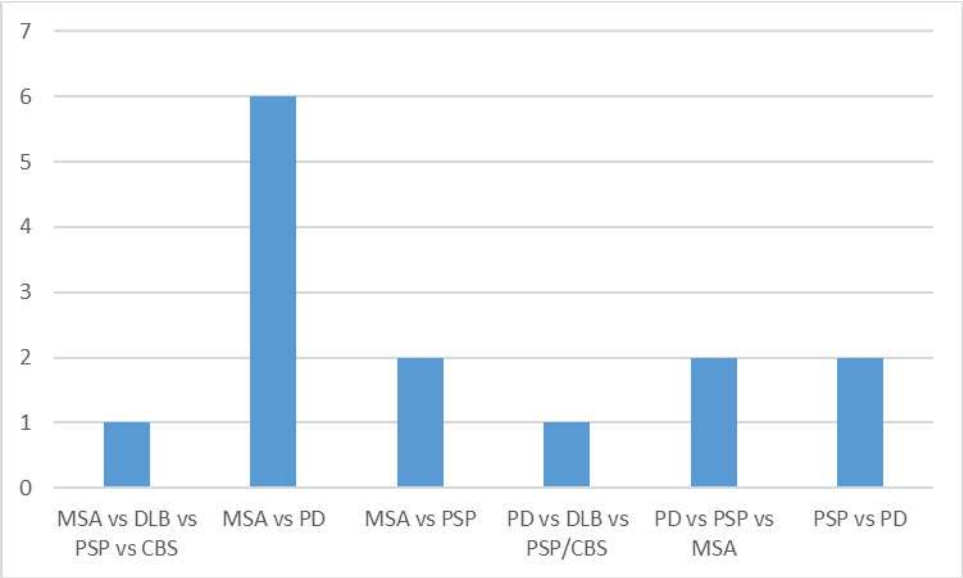

Fig. 15 Diagnoses analyzed in "PD vs PSP vs MSA" category

Multimodal and instrumentation:

Given the mixed nature of the symptoms present in the diseases discussed in this section, both MS and NMS, the diagnostic modalities are different and there is no clear prevalence of one over the others. Three studies focused on video modalities (Amboni et al., 2021; Gandor et al., 2020; Zhou et al., 2021) and three on movement (Amboni et al., 2021; Belic et al., 2023; Wu et al., 2022); note that one of these (Amboni et al., 2021) supported both modalities. Furthermore, three other studies performed differential diagnosis by means of voice analysis (Das et al., 2019; Li et al., 2018; Kowalska-Taczanowska et al., 2020), while three others performed electrophysiological tests (Hu et al., 2023; Yamamoto et al., 2017; Leys et al., 2020). Finally, three studies relied on cognitive tests and questionnaires (Schröter et al., 2023; El Otmani et

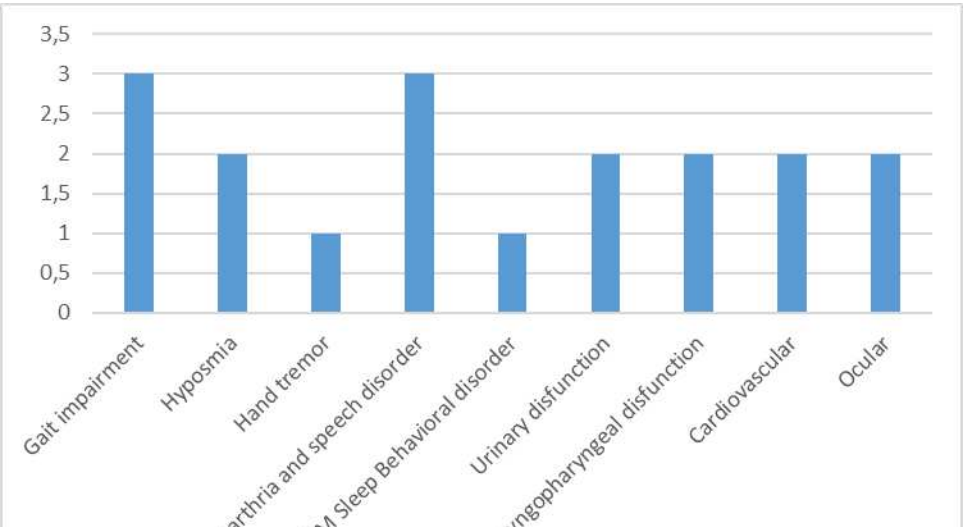

Fig. 16 Symptoms treated in "PD vs PSP vs MSA"

al., 2023; Shill et al., 2021).

In terms of sensors, we also find here an absence of prevalence of one type of sensor over the others: optical (21%), inertial (14%), acoustic (21%) and electrical sensors (21%). In addition, four studies (Amboni et al., 2021; Belic et al., 2023; Li et al., 2018; Wu et al., 2022) made use of wearable devices.

Optical sensors have been used in three studies. In Zhou et al. (2021) a binocular EyeLink system (Bao Runtong Research Ltd. China) was used for video-oculographic eye movement recordings, while in Gandor et al. (2020) they executed an endoscopic evaluation using 3.9-mm-diameter (ENF-VH, Olympus, Shinjuku, Japan) or 3.5-mm-diameter (Storz 11101 RP2, Karl Storz, Tuttlingen, Germany) flexible fiberoptic rhinolaryngoscope with a video processor (CV-170, Olympus, Shinjuku, Japan), and processing software (rpSzene 10.7 g on Panel-PC-226/227, Rehder/Partner, Hamburg, Germany), or a 2.9-mm-diameter flexible fiberoptic rhinolaryngoscope (CMOS, Karl Storz, Tuttlingen, Germany) with a portable video processor (CMAC, Karl Storz, Tuttlingen, Germany) linked to a 19" flat screen monitor (9519NB, Karl Storz, Tuttlingen, Germany). Then, in Amboni et al. (2021) they have made use of a wearable system supporting both movement and video modalities: BTS Engineering Smart DX (optical system equipped with six infrared cameras, two video cameras, two force plates, a set of passive markers, and an elaborator).

Inertial sensors have been used in two studies and both integrated them in wearable devices. In Belic et al. (2023) a wearable system was developed based on inertial sensors that capture the movements of fingers during repetitive finger tapping, in treating hand tremor, while in the study of Wu et al. (2022) a specialized hardware system consist of a hub control unit, 4 inertial sensor units, and a transmission node was implemented, as shown in Fig. 17. The inertial sensor units are based on the Invensense MPU9250 chip, measure 22 × 18 × 6 mm and weight 1.8 g for each unit. Each sensor unit could record tri-axial acceleration (ACC, ±8g), and angular velocity (AV, ±2000 deg/s) with a sampling rate of 100 Hz; the hub control unit measures 39 ×41× 11 mm and weighs 38.2 g, which contains a MPU9250 and a nRF52832 to synchronize all collected data and transmit them to the transmission node using Bluetooth; and the transmission node, i.e., IK-52832DK, transports all collected data to the master computer with wired connection for gait characteristic analysis. The sensor units are laterally attached to the patients' upper quarter of the tibia in shanks and first cuneiform in feet with velcro elastic belts, while the hub control unit is connected by velcro belt to the lumbar vertebra.

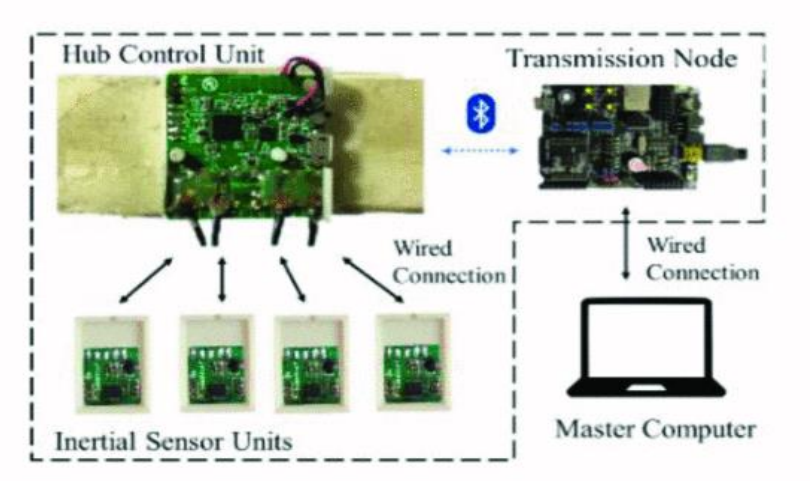

Fig. 17

Then acoustic sensors were taken into account in 21% of the studies. In Kowalska-Taczanowska et al. (2020) voice samples were recorded in a soundproof laboratory, with an average noise level of maximum 30 dB, using a large membrane multidirectional microphone, with bandwidth of 40 Hz–18 kHz, sensitivity 10 mV/pa, threshold sound pressure level 142 dB, and dynamic range 119 dB. During the recording, the microphone was on a support stand, at the level of the patient's mouth, at a distance of 20 cm (±5 cm). The acoustic signal was digitally processed using a 24-bit preamplifier M-Audio M-Track and saved on the hard drive of a computer running on a 64-bit operating system. While in Li et al. (2018) and Das et al. (2019) they used a head-mounted condenser microphone (Bayerdynamic Opus 55, Heilbronn, Germany) situated approximately 5 cm from the mouth of each subject.

Electrical sensors were also used in three studies, regarding electrophysiological tests. In Yamamoto et al. (2017) the following tests were performed: Sphincter Electromyography (EMG): Used to evaluate neurogenic changes in the anal sphincter muscle, providing valuable information for differentiating MSA from PD; External Anal Sphincter (EAS)-EMG, a specific type of sphincter EMG used to evaluate neurogenic changes in the anal sphincter muscle; Post-void Residual Urine Volume (PVR) Measurement, a measure helpful for differentiating MSA from PD; Pressure-flow Study (PFS), performed to evaluate bladder contractility, providing additional insights into differentiating MSA from PD. In Leys et al. (2020) they used electrical sensors for beat-to-beat finger-cuff BP recording and impedance cardiography (Task Force® Monitor, TFM), while in Hu et al. (2023) EAS-EMG and other tests were performed by using Keypoint electromyography/evoked potential instrument (Vidi, Denmark).

Finally, in three cases the studies were performed through cognitive and other tests: in Schröter et al. (2023) a modified version of the Delphi study was proposed, in El Otmani et al. (2023) they used the REM sleep behavior disorder screening questionnaire, while in Shill et al. (2021) hyposmia was treated with UPSIT test (University of Pennsylvania Smell Identification Test), an olfactory test that requires subjects to identify, by multiple-choice, 40 odorants microencapsulated on “scratch and sniff” labels.

Results:

In Zhou et al. (2021) they explored using eye movement patterns to distinguish PD from MSA. Oculomotor symptoms overlapped, but the multiple-step pattern (MSP) shows potential in PD diagnosis. However, MSP occurred in both diseases, reducing specificity. Reflexive saccade tests indicate differences in hypometria and hypermetria, suggesting potential for distinguishing MSA from PD. In Gandor et al. (2020) they used the MSA-FEES task to evaluate laryngeal motion abnormalities in MSA patients, finding them prevalent before clinical symptoms, with 93% affected. Irregular arytenoid cartilage movements (iACM) were common. Early dysfunction was independent of subtype or disease duration, supported by MRI. Systematic laryngeal assessment, focusing on iACM, may enhance MSA diagnosis over PD. Then, the study of Amboni et al. (2021) demonstratesd that quantitative gait evaluation clearly distinguishes PSP patients from PD patients since the earliest stages of disease. Our findings indicate that gait analysis could be candidate as a reliable biomarker in both clinical and research setting. In addition, the work offers speculative clues for conceiving early disease-specific rehabilitation strategies. In Belic et al. (2023) they employed kNN classification on gyroscope data from finger tapping to diagnose PD and atypical

parkinsonisms, achieving 85.18% accuracy. It identified MSA and healthy controls most effectively, highlighting gyroscope metrics' diagnostic potential despite data limitations for deep learning. Collaboration in data collection is recommended for clinical adoption. Then in the study of Wu et al. (2022) they found distinct gait differences between MSA and PD patients, including stride variability and step time asymmetry favoring MSA. However, clinical alignment was lacking, attributed to small sample sizes and classification model improvements needed for accurate diagnosis. The study of Kowalska-Taczanowska et al. (2020) examined speech disorders in PD, PSP, and MSA patients, highlighting common dysarthria features and voice impairments. APS patients, particularly MSA, exhibited severe voice handicap, contrasting with milder impairment in PD. In the self-assessment of voice handicap, voice impartment was more frequent and severe in APS patients that in PD patients. In 86.67% of MSA patients, speech disorders were reported as severe and moderate. Among PSP patients, 80% reported moderate and severe voice impairment, whereas in most PD patients (56.67%) voice impartment was mild. Furthermore, Li et al. (2018) introduced a machine learning approach for PSP and MSA diagnosis using FDA and LR, enhancing accuracy to 80%. It emphasizes interpretability and generalization despite limited data, needing validation from larger datasets and ongoing research. While Das et al. (2019) developed disease-specific speech features for early Parkinsonism diagnosis, focusing on MSA and PSP. Using machine learning on a small dataset, FDA establishes a scalar variable combining hypokinetic and ataxic speech traits. Gaussian or 1d SVM classifiers achieve 88% accuracy with LOSO training, marking progress in PSP and MSA differentiation. Further validation with larger datasets is ongoing. Yamamoto et al. (2017) compared post-void residual (PVR) measurement and anal sphincter EMG in diagnosing MSA versus PD. PVR during pressure-flow study (PFS) showed superior diagnostic utility over sphincter EMG mean duration of motor unit potentials (MUPs). Challenges include clinician unfamiliarity with urinary dysfunction assessment. The study of Leys et al. (2020) aimed to use CAFT to distinguish MSA-P from PD but found low reliability, especially with nOH present. Despite differences in some autonomic features, CAFT generally failed to differentiate between the two diseases, aligning with prior research. While in Hu et al. (2023) the study emphasized the difficulty in distinguishing MSA from PD based on motor symptoms alone and highlighted the importance of electrophysiological indicators, which enhanced diagnostic accuracy and robustness. Combining BCR and EAS-EMG indicators showed promise, achieving high sensitivity and specificity, especially in males and females. In Schröter et al. (2023) the modified Delphi study was performed by seven specialists effectively categorized PD and atypical parkinsonian syndromes, highlighting rapid progression and distinct symptoms. It emphasized integrating paraclinical information for accurate diagnosis and continuous guideline refinement, demonstrating the study's robustness and diagnostic relevance. In El Otmani et al. (2023) RBD and hyposmia as critical premotor symptoms in PD and DLB were highlighted, emphasizing their early diagnostic value and neuroprotective implications (Specificity for: RBD 100%, hypersmia: 90%; Sensitivity for: RBD 76%, hypersmia 92%). Despite single-center limitations, it confirms higher incidence in PD and DLB compared to tauopathies, urging further research. Finally in Shill et al. (2021) the UPSIT for olfaction in PSP and PD showed distinctive patterns, though not differentiating PSP from PD. PSP sometimes mirrored control scores, suggesting preserved olfaction. However, significant differences among PSP, PD, and controls indicate UPSIT's diagnostic potential with comprehensive clinical assessment (Specificity 81.4%; Sensitivity 84.5%).

4.3.4. PD

Data source and sample size:

In this case, the research studies analyzed used private data sets, except for Yuan et al. (2021) which used to separate datasources one public (The Partners Healthcare Research Patient Data Registry, composed of electronic medical records (EMR) from approximately 6 million individuals in Massachusetts. Data used in this study covers patient records from the early 1990s through the end of 2018) and one private (A de-identified administrative claims database from a large private insurance company representing more than 75 million unique members during a period extending from January 1, 2008 through December 31, 2018. Members with zip codes in Massachusetts were excluded).

The number of patients enrolled in the various studies ranges from a minimum of 19 to a maximum of 50318 (mean: 6429.25, median: 76.5). In general, most of the studies (62%) involved fewer than 100 patients, with only one study involving more than 1000 patients. Here 9 studies have been reviewed.

The diagnoses studied focused on the analysis of idiopathic PD, so this section it isn't properly into differential diagnosis, but works have been taken into consideration that have the potential to be further developed and conducted in differential diagnosis studies in the future.

Symptoms:

The symptoms discussed here are among the most common in idiopathic PD, with motor symptoms (77%) predominating over non-motor symptoms (23%), Fig. 18. The most frequent symptoms include gait impairment (Yuan et al., 2021; Martinez et al., 2018), tremor disorder (Yuan et al., 2021; Varghese et al., 2021; Marino et al., 2019) and dysarthria (Ali et al., 2019; Karlsson et al., 2019). In contrast, the least analyzed symptoms were hypomimia (Guan, 2021) and disorders of a cognitive and neuropsychological nature (Turner et al., 2023; Weyhenmeyer et al., 2020).

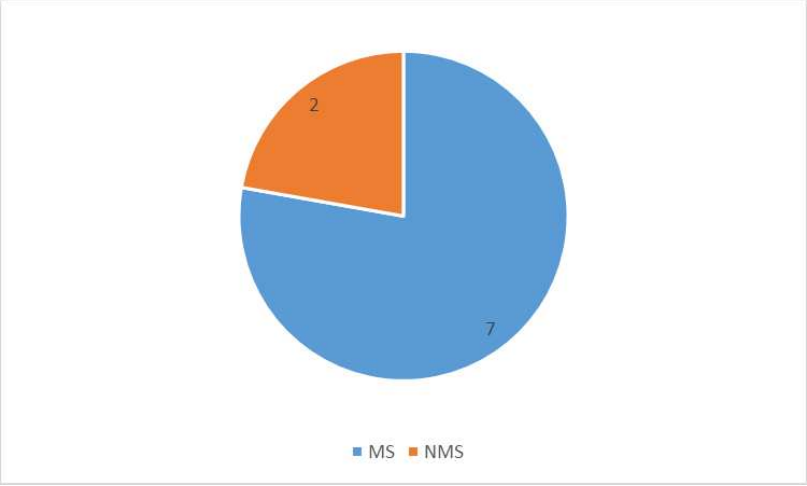

Fig. 18 MS vs NMS in "PD" section

Multimodal and instrumentation:

As the symptoms of idiopathic PD are predominantly motoric, it is not surprising that the most commonly used diagnostic modality is movement (55%) (Yuan et al., 2021; Martinez et al., 2018; Weyhenmeyer et al., 2020; Varghese et al., 2021; Marino et al., 2019). Other lesser-used modalities were video (Guan, 2021; Weyhenmeyer et al., 2020) and voice (Ali et al., 2019; Karlsson et al., 2019), at 22% each. Finally, one case of electrophysiological testing

(Weyhenmeyer et al., 2020) and one of cognitive testing (Turner et al., 2023) were also studied.

Regarding the technological instrumentation used, inertial, optical, electrical and acoustic sensors were used almost equally, while wearable devices were used in 33% of the studies.

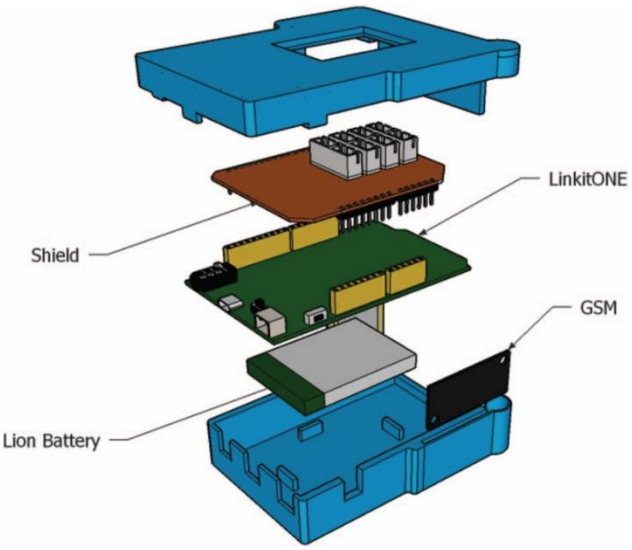

Fig. 19

There were two studies that used inertial sensors. In Varghese et al. (2021) they performed measurements through smartwatches (Apple Watch 3, Apple Watch 4), included in a Smart Devis System that also includes a smartphone, and using accelerometers (smartwatches), seismometer and high-precision shaker (gold standard sensor validation).Then, the system used in Marino et al. (2019) for tremor recording was a card Linkit ONE and an array of 4 3-axis accelerometers ADXL345 (Analog Devices). The ADXL 345 is a small, thin, ultra-low power, 3 axis accelerometer with high resolution (13-bit) measurement at up to ±16g. Digital output data is formatted as 16 bit two's complement and is accessible through either a SPI (3 or 4 wire) or I2C digital serial interface. The platform is equipped with a GPS positioning system, able to geo-reference data from the accelerometer and send them via Bluetooth. The core of the system is based on the MediaTek MT2502 system-on-chip; with a processor ARM7 EJ-S 260MHz and a memory of 4MB RAM and 16 MB Flash, equipped with long battery life (3.8V 5100mAh). The system has the size of a cigarette packet and the enclosure is assembled in a 3D printed polylactic acid version, the design of the version with the array of 4 accelerometers and its realization is shown in Fig. 19 and Fig. 20, respectively.

Fig. 20

In Guan (2021) facial action units in PD patients were extracted using OpenFace, a CMU MultiComp containing features like face keypoint detection tracking, head pose estimation, perspective detection tracking and AU unit detection, and containing a facial behavioral analysis framework for training and detecting all sources. Then in Weyhenmeyer et al. (2020), EEG data were collected using a 64-channel cap (Biosemi ActiveTwo) with additional EOG and EMG electrodes. Data were recorded at 512 Hz and

referenced to the mastoid electrodes. Head position was tracked using an electromagnetic system (Polhemus FASTRAK). Two haptic robots tracked thumb and finger movements and provided haptic feedback. Eye movements were recorded using an EyeLink 1000 eye-tracker at 1000 Hz. All behavioral and EEG data were synchronized. In Martinez et al. (2018) they used pressure sensors implemented in the F-scan in-shoe pressure measurement system (Tekscan, Boston, MA, USA) that included 0.15 mm flexible insoles with a resolution of four sensors per square centimeter and a total of 954 sensors per insole (pressure data on both plantar surfaces were collected using the F-scan in-shoe pressure measurement system). While in Ali et al. (2019) the study was carried out with the use of acoustic sensors, a Trust MC-1500 microphone was used for speech recordings.

Results:

In Yuan et al. (2021), the study's machine learning model, using gait and tremor disorders as diagnostic points, achieved a validation AUC of 0.874, indicating high accuracy. It allowed for earlier PD diagnosis and guides clinical decisions, though primarily driven by pre-existing clinician suspicions of PD. The study of Martinez et al. (2018) found that insole sensors effectively differentiated gait characteristics in mildly affected PD patients, showing increased double support time variability, asymmetry, and lower phase stability. The LDA classifier had an accuracy of 64.1%, sensitivity of 47.1%, and specificity of 77.3%, indicating moderate robustness. In Weyhenmeyer et al. (2020) they found that Delay Differential Analysis (DDA) effectively distinguished between PD patients and controls, with kinematic and EEG data combined enhancing classification accuracy. High-density EEG caps further improved classification. Despite promising results, the study's limited sample size necessitates larger studies for validation. In Varghese et al. (2021), the study validated smartwatch sensors for monitoring tremors, achieving high diagnostic accuracy (above 80%) in simple tasks but lower (67%-74%) in distinguishing Parkinson's from similar disorders. Despite sample size limitations, it advances digital biomarkers, requiring further quality assurance and regulatory approval. The study of Marino et al. (2019) highlighted the effectiveness of a novel tremor assessment device, showing precision in measuring tremor frequency (4-6 Hz), involving 41 PD patients under stress conditions. It demonstrates the potential for clinical and home use, enhancing diagnostic accuracy and reliability for Parkinson's disease. Guan (2021) found logistic regression outperforms KNN in identifying PD through facial expression disorders, with an accuracy of 90.06%. Despite effective symptom evaluation, limitations include data constraints and small sample size, suggesting future research should expand datasets and explore deep learning methods for better patient identification. In Ali et al. (2019) the study's hybrid intelligent system for detecting PD achieved high accuracy, with 95% on training and 100% on testing using all features. After addressing gender imbalance, accuracies were 80% for training and 82.14% for testing, indicating robust diagnostic potential. Karlsson et al. (2019) demonstrated that acoustic analysis of Diadochokinetic (DDK) syllables can distinguish PD speakers from controls and predict reduced articulatory precision with up to 93% accuracy. The /ka/ syllable was most informative. Despite its efficacy, the study's robustness is limited by the need for larger sample sizes and automation for clinical use. Finally, the study of Turner et al. (2023) found minimal cognitive decline over 5 years in PD patients with baseline MoCA > 26, except for modest working memory decline. Lower baseline MoCA $\leq$ 26 predicted worse initial performance but no accelerated decline. The study highlights limitations in cognitive screening cutoffs and recommends focusing on working memory tasks in trials.

4.3.5. Other diagnoses

Data source and sample size:

The research studies analyzed used private data sets, except for Khoury et al. (2019). The gait dataset used in this study was obtained from the PhysioNet web site. It contains gait data for 93 patients suffering from Parkinson's disease and 72 healthy subjects. 4 studies were here reviewed.

The number of patients enrolled in the various studies ranges from a minimum of 14 to a maximum of 165 (mean: 61, median: 32.5). In general, most of the studies (75%) involved fewer than 100 patients, with only one study involving more than 100 patients.

The diagnoses in this section are only four. They were not classifiable for any of the previous sections but are nevertheless included in the collection of this systematic review work, due to the presence of idiopathic PD, atypical parkinsonisms or secondary parkinsonisms: PD (vs ALS vs HD), PD vs SWEDD (Scans Without Evidence of Dopaminergic Deficit), PD vs VaP (Vascular Parkinsonism) and PSP vs anti-IgLON5.

Symptoms:

The symptoms discussed here are all MS. The most frequent symptoms include gait impairment (Khoury et al., 2019; Fernandes et al., 2018). Then one study is about tremor disorder (Kwon DY et al., 2023) and one treated ocular disfunctions (Macher et al., 2021), Fig. 21.

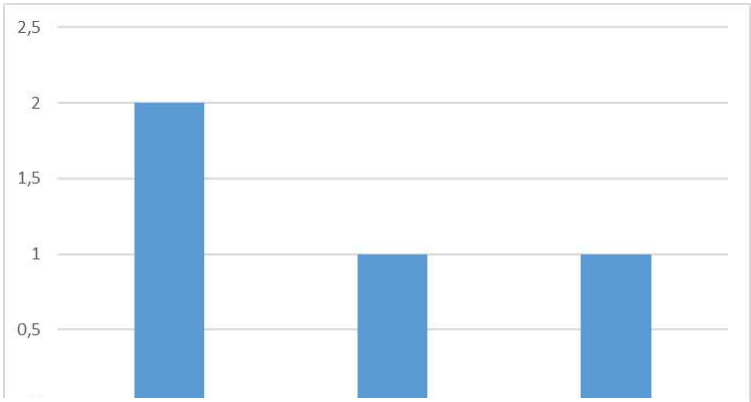

Fig. 21 Symptoms analyzed in "Other diagnoses"

Multimodal and instrumentation:

The symptoms discussed in this section are all motor. Consequently, the diagnostic modalities used all focus on movement (Khoury et al., 2019; Fernandes et al., 2018; Kwon DY et al., 2023) or video parameters (Macher et al., 2021).

The instrumentation used includes inertial sensors (implemented in wearable devices), electrical or optical sensors.

In Khoury et al. (2019) vertical ground reaction force (vGRF) measurements were collected from eight force sensors (Ultraflex Computer DynoGraphy, Infotronic Inc., Hong Kong, China) placed under each foot of the subjects. Kwon DY et al. (2023) implemented gyroscopes in wearable measurement system based on 3-axis gyro sensors (L3G4200D, STMicroelectronics, Aschheim city, Germany), while Fernandes et al. (2018) used two Physilog 0 inertial sensors (Gait Up 0, Switzerland) positioned on both feet were used to measure 22 gait variables of each stride. Finally, Macher et al. (2021) made use of Video-oculography (VOG) and a rotational chair system.

Results:

The study of Khoury et al. (2019) The study shows high effectiveness and robustness in diagnosing PD using gait patterns, achieving 92.86% accuracy in distinguishing PD from ALS and 83.33% from HD. Classifiers perform best in the Hausdorff sub-dataset, particularly for high-severity PD cases. The clinical-based method outperforms others, highlighting the importance of clinical features in PD diagnosis. Kwon DY et al. (2023) showed SWEDD patients have distinct tremor patterns compared to PD patients, with slower, smaller tremors in pitch direction. Quantitative data and robust diagnostic methods, including tremor amplitude analysis, provide a solid basis for diagnosis. Significant statistical evidence and comparisons with previous studies confirm its reliability. Further research on different tremor types is recommended for comprehensive differentiation. In Fernandes et al. (2018) they demonstrated that artificial neural network classifiers, specifically Multilayer Perceptrons (MLPs) and Deep Belief Networks (DBNs), effectively distinguished Parkinson's disease patients from controls using gait data from wearable sensors. MLPs achieved up to 95.68% accuracy, while DBNs reached 94.17%. DBNs outperformed MLPs in differentiating vascular parkinsonism from idiopathic Parkinson's disease. Despite sample size limitations, the study's robust methods and significant findings highlight its efficacy in classifying gait-based neurological conditions. Finally, Macher et al. (2021) used Video-Oculography (VOG) to investigate abnormal eye movements in anti-IgLON5 disease, highlighting distinct saccade characteristics compared to PSP and healthy controls. Key findings include more square wave jerks in PSP and spontaneous nystagmus in anti-IgLON5 patients. Despite limitations like small sample size, the study demonstrated that VOG could differentiate anti-IgLON5 disease from PSP, suggesting its potential as a diagnostic tool. Further research is needed to validate these findings.

5. Discussion

In discussing the findings and implications of systematic reviews focusing on the differential diagnosis of parkinsonian disorders, several critical challenges and avenues for future research emerge. These challenges span across data collection, study selection, and data analysis, each significantly impacting the reliability and generalizability of systematic review outcomes.

Firstly, the comparison between Alzheimer's Disease (AD) and Dementia with Lewy Bodies (DLB) highlights substantial hurdles. The primary issue lies in the reliance on limited sample sizes from private datasets, predominantly sourced from public hospitals and specialized clinics. This approach restricts the diversity of patient demographics, undermining the broader applicability of findings. Most studies reviewed involved fewer than 400 patients, which compromises statistical power and the robustness of conclusions. Methodological discrepancies in cognitive assessments like the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) further complicate data synthesis and comparative analyses, hindering efforts to establish consistent diagnostic criteria (Ala et al., 2022; Yamamoto et al., 2017).

Similar challenges are evident in the differentiation between Parkinson's Disease (PD) and Essential Tremor (ET). Studies often draw from small, private datasets with fewer than 100 patients per study, limiting the generalizability of results. The focus on motor symptoms, characteristic of both disorders, neglects the comprehensive evaluation of non-motor symptoms crucial for accurate diagnosis. Moreover, the introduction of diverse technological tools such as inertial sensors and accelerometers introduces variability, necessitating rigorous validation across different study settings (Shahtalebi et al., 2021; Sushkova et al., 2020).

The complexity amplifies when comparing PD with Progressive Supranuclear Palsy (PSP) and Multiple System Atrophy (MSA). The overlap in symptoms complicates differential diagnosis, exacerbated by varying sample sizes and methodological approaches across studies. Diagnostic tools ranging from video analysis to electrophysiological tests contribute to methodological heterogeneity, requiring sophisticated statistical techniques like meta-regression to reconcile disparities and enhance result reliability (Xie et al., 2015; Koga et al., 2015).

To address these challenges effectively, future systematic reviews could leverage emerging technologies and methodologies to complement traditional diagnostic approaches. For instance, integrating advanced imaging modalities such as magnetic resonance imaging (MRI) and positron emission tomography (PET) could provide deeper insights into disease pathology and aid in distinguishing between closely related conditions like AD and DLB (Azar et al., 2020). These technologies not only offer a more precise assessment of structural and functional brain changes but also facilitate earlier and more accurate diagnosis, potentially optimizing therapeutic interventions tailored to disease progression stages.

Furthermore, enhancing the reporting standards of systematic reviews, particularly in terms of diagnostic accuracy metrics such as sensitivity, specificity, and predictive values, is paramount. Standardized reporting guidelines, akin to those recommended by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), would ensure

transparency and consistency across studies, facilitating more robust comparisons and meta-analyses (Maraolo, 2022)

Improving patient datasets represents another crucial frontier. By expanding collaborative efforts in data sharing and pooling resources from diverse clinical settings, researchers can overcome the limitations of small, homogeneous sample sizes. This approach not only enhances statistical power but also broadens the demographic and clinical spectrum, strengthening the external validity and applicability of findings (Fernandes et al., 2018).

Moreover, advancements in diagnostic instrumentation are pivotal. Validating and standardizing the use of wearable technologies, smart sensors, and biomarker assays could revolutionize diagnostic paradigms, offering continuous monitoring capabilities and personalized treatment strategies (Cheng et al., 2022; Martinez et al., 2018). Integrating these innovations into longitudinal studies would provide invaluable insights into disease progression dynamics and therapeutic efficacy over time, addressing current gaps in understanding longitudinal disease trajectories (di Biase et al., 2017).

In conclusion, while systematic reviews provide critical insights into the differential diagnosis of parkinsonian disorders, they are challenged by inherent limitations in data quality, methodological variability, and diagnostic tool efficacy. Future research endeavors should focus on harnessing emerging technologies, enhancing reporting standards, optimizing patient datasets, and standardizing diagnostic methodologies to advance diagnostic accuracy and clinical management in neurodegenerative diseases. These efforts are essential for translating research findings into tangible improvements in patient care and outcomes across diverse neurological conditions.

6. Conclusions

The findings and implications of systematic reviews focused on the differential diagnosis of parkinsonian disorders and neurodegenerative diseases like Alzheimer's. These themes underscore the pressing need for advancements in diagnostic methodologies, data quality, and technology integration to overcome existing challenges and enhance clinical outcomes.

Firstly, the imperative for clear, precise, and cost-effective differential diagnosis has spurred the development of novel diagnostic modalities. Current systematic reviews reveal significant hurdles related to sample sizes and data sources, predominantly relying on limited datasets from private institutions. This reliance compromises the diversity of patient demographics and the generalizability of findings across broader populations.

Moreover, the review highlights the methodological disparities in cognitive assessments and diagnostic criteria across studies, hindering consistent comparisons and synthesis of results. Addressing these challenges necessitates standardized reporting guidelines, akin to PRISMA principles, to ensure transparency and reproducibility in future studies

Advancements in diagnostic instrumentation, particularly the integration of advanced imaging modalities like MRI and PET, hold promise for improving diagnostic precision. These technologies offer insights into structural and functional brain changes, aiding in the differentiation of closely related conditions such as Alzheimer's and Lewy Body Dementia.

Looking ahead, future systematic reviews should prioritize the validation and standardization of wearable technologies and biomarker assays. These innovations enable continuous monitoring and personalized treatment strategies, crucial for understanding disease progression and optimizing therapeutic intervention.

In conclusion, while systematic reviews provide invaluable insights into the differential diagnosis of neurodegenerative diseases, they underscore the need for robust methodologies, enhanced data sources, and advanced technologies. By addressing these challenges, future research can advance diagnostic accuracy, improve patient care outcomes, and pave the way for more effective treatments across diverse neurological conditions.

Acronyms

PD	Parkinson’s disease
AP	Atypical parkinsonism
AD	Alzheimer’s disease
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
MS	Motor symptoms
NMS	Non-motor symptoms
ET	Essential tremor
DLB	Dementia with Lewy Bodies
MSA	Multiple system atrophy
PSP	Progressive supranuclear palsy
CBS	Corticobasal syndrome
QEEG	Quantitative electroencephalography
EEG	Electroencephalography
ECG	Electrocardiography
EMG	Electromyography
DaTscan	Dopamine Transporter Scan
MRI	Magnetic Resonance Imaging
CT	Computed Tomography
PET	Positron emission tomography
SPECT	Single-photon emission compute tomography
DBS	Deep Brain Stimulation
SP	Secondary Parkinsonism
MMSE	Mini-Mental State Examination
ACE-III	Addenbrooke's Cognitive Examination III
ACE-R	Addenbrooke's Cognitive Examination-Revised
TMB	Temporary memory binding
DFV	Dominant frequency variability
TSI	Tremor Stability Index
EAS-EMG	External Anal Sphincter EMG
PVR	Post-void Residual Urine Volume

PFS	Pressure-flow Study
MSP	Multiple-step pattern
DDA	Delay Differential Analysis
vGRF	vertical Ground Reaction Force
MLP	Multilayer Perceptron
DBN	Deep Belief Network

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Appendix A: AD vs DLB Table Results

Authors	Participants	Diseases	Symptoms	Modal	Instrumentation (WD: Wearable Device)	Specificity	Sensitivity	p-value	Accuracy
Azar et al.	51: 34 AD, 17 AD mixed DLB	AD DLB	Early dementia	Cognitive test		Phonemic fluency: 27.3% TMT-A: 36.4% Pentagon copy: 72.7%	Phonemic fluency: 96.4% TMT-A: 92.9% Pentagon copy: 75%	Phonemic fluency: p=0.029. TMT-A: p=0.03. Pentagon copy: p=0.003.	
Yamada et al.	123: 47 AD, 27 DLB, 49 CN (cognitively normal)	AD DLB	MCI Dementia Handwriting	Movement	Electrical sensors (Digitizing tablet and pen)				AD vs CN: 79.1% LBD vs CN: 85.3% AD vs LBD: 73.8% Three-class classification model (AD, LBD, and CN): 68.6%

Galvin et al.	342: 53 controls, 78 AD, 110 DLB, 79 mild cognitive impairment due to AD (MCI-AD) and 22 MCI-DLB	AD DLB (MCI-AD MCI-DLB)	Autonomic features, cognitive fluctuations, sleep disturbances, extrapyramidal signs, hallucinations, anxiety, apathy, and visual illusions	Cognitive test				p<.001: Indicates a significant difference between DLB and AD in CDR, FAQ, and NPI scores p=.001 and p=.002: Indicate significant differences in FAQ scores between DLB and AD p<.001: Indicates a significant presence of hallucinations in DLB patients compared to AD patients p<.001: This p-value indicates a significant difference in bradykinesia, rigidity, postural instability, and resting tremor scores in DLB patients compared to AD patients	

Mc Ardle et al.	110: 29 controls, 36 AD, and 45 LBD [30 DLB and 15 PDD]	AD DLB	Gait impairment Cognitive impairment	Movement / Cognitive	Electrical sensors (Pressure sensor)	40%	73%	P-value: ≤ .001	Modest (0.6-0.7)
Tsujimoto et al.	3093: 2683 AD, 410 DLB	AD DLB	MCI	Cognitive test		Group A: 0.816 Group B: 0.816 Group C: 0.895	Group A: 0.641 Group B: 0.575 Group C: 0.462		
Suzuki et al.	39: 18 DLB, 21 AD	AD DLB	MCI	Quantitative EEG	Electrical sensors	85.7% (63.7–97.0%) After excluding participants taking >5 mg donepezil: 89.5% (66.9–98.7) When limiting participants taking any cholinesterase inhibitors at less than half of the maximum approved doses in Japan: 86.7% (59.5–98.3)	72.2% (95% CI 46.5–90.3%) After excluding participants taking >5 mg donepezil: 83.3% (95% CI 51.6–97.9) When limiting participants taking any cholinesterase inhibitors at less than half of the maximum approved doses in Japan: 83.3% (95% CI 51.6–97.9)		79.5% (63.5–90.7%) After excluding participants taking >5 mg donepezil: 87.1% (70.2–96.4) When limiting participants taking any cholinesterase inhibitors at less than half of the maximum approved doses in Japan: 85.2% (66.3–95.8)
Prats-Sedano et al.	182: 76 DLB, 40 AD, 66 Healthy controls	AD DLB	Dementia	Cognitive test		Differentiating dementia from non-dementia 88% Differentiating DLB from AD using 'memory/visuospatial' ratio 68% Differentiating DLB from AD using logistic regression model 63%	Differentiating dementia from non-dementia 96% Differentiating DLB from AD using 'memory/visuospatial' ratio 82% Differentiating DLB from AD using logistic regression model 78%		Differentiating DLB from AD using 'memory/visuospatial' ratio 77% Differentiating DLB from AD using logistic regression model 74%

Mehrarm et al.	96: 18 HC (11 male, 7 female), 32 AD (22 male, 10 female), 25 DLB (20 male, 5 female) and 21 PDD (20 male, 1 female)	AD DLB PDD	MCI	EEG	Electrical sensors	DLB vs. AD: 100% LBDs vs. HC: 100%	DLB vs. AD: 47% LBDs vs. HC: 59%		DLB vs. AD: 66% (±13%) LBDs vs. HC: 76% (±12%)
Ala et al.	400: 136 AD, 24 DLB, 240 others	AD DLB	Dementia	Cognitive test		Equation P-M = 1 (Pentagon-copying subscale score minus Memory subscale score): 92% Equation P-M < 0: 85% Pentagon-copying subscale (P): 67% Memory subscale (M): 54% The pentagon-copying test graded by the QSPT method showed: 73%	Equation P-M = 1 (Pentagon-copying subscale score minus Memory subscale score): 43% Equation P-M < 0: 46%		

Beach et al.	257: ADD (n = 66) ADD/DLB (n = 29) ADLB N = 30) PDD+AD (n = 21) PDD-AD (n = 27) Control (n = 84)	AD DLB PDD	Hyposmia	Olfaction test		First UPSIT Score (cutoff: < 20) 64.6% Mean UPSIT Score (cutoff: < 17) 71.9% Matched Year Hallucinations 96.9% Matched Year Parkinsonism 77.1% Cumulative Hallucinations 76.0% Cumulative Parkinsonism 45.8%	First UPSIT Score (cutoff: < 20) 93.1% Mean UPSIT Score (cutoff: < 17) 86.2% Matched Year Hallucinations 17.2% Matched Year Parkinsonism 31.0% Cumulative Hallucinations 51.7% Cumulative Parkinsonism 65.5%	First UPSIT Score (cutoff: < 20) p-value: < 0.0001 Mean UPSIT Score (cutoff: < 17) p-value: < 0.0001 Matched Year Hallucinations p-value: 0.0905 Matched Year Parkinsonism p-value: 0.2648 Cumulative Hallucinations p-value: 0.0106 Cumulative Parkinsonism p-value: 0.3001	First UPSIT Score (cutoff: < 20) 71.2% Mean UPSIT Score (cutoff: < 17) 75.2% Matched Year Hallucinations 78.4% Matched Year Parkinsonism 66.4% Cumulative Hallucinations 70.4% Cumulative Parkinsonism 50.4%
Yamamoto et al.	130: AD (n = 57) DLB (n = 73)	AD DLB	Dementia	Cognitive test				Clock contour: P = .037 Number placement: P < .001 Overall clock drawing score: P < .001 Delayed recall: P < .001	
Van Dyk et al.	140: pAD (n = 124) DLB (n = 17)	AD DLB	Dementia (Fluctuating cognition (FC))	Cognitive test		For RAs' ratings (FC severe): 95% For MDs' ratings (FC severe): 96%	For RAs' ratings (FC severe): 57% For MDs' ratings (FC severe): 70%		

Mamiya et al.	124: DLB (n = 52) AD (n = 52) HC (n = 20)	AD DLB	Visual hallucinations	Pareidolia test		92%	81%	p < 0.01 for differences between DLB, AD, and HC groups.	
Peraza et al.	89: HC (N = 17) AD (N = 26) DLB (N = 25) PDD (N = 21)	AD DLB PDD	Dementia	EEG	Electrical sensors	AD vs DLB: 85% DLB vs PDD: 76% HC vs AD + DLB: 77%	AD vs DLB: 80% DLB vs PDD: 76% HC vs AD + DLB: 96%		
Stylianou et al.	73: Controls (N = 21) AD (N = 18) DLB (N = 17) PDD (N = 17)	AD DLB PDD	Dementia	Quantitative EEG	Electrical sensors (Wearable device: 128 channel ANT Waveguard caps (ANT Neuro, Netherlands)	AD vs DLB: 83.3%	AD vs DLB: 92.26%		
Garn et al.	61: AD (N = 20) FTDbv (N = 21) PDD/DLB (N = 20)	AD DLB PDD bvFTD (frontotemporal dementia, behavioral variant)	Dementia	Quantitative EEG	Electrical sensors	AD vs DLBPD: 100% AD vs bvFTD: 100% bvFTD vs DLBPD: 100%	AD vs DLBPD: 100% AD vs bvFTD: 100% bvFTD vs DLBPD: 100%	AD vs DLBPD: p = 6.80e-08 AD vs bvFTD: p = 7.21e-8 bvFTD vs DLBPD: p = 2.53e-5	AD vs DLBPD: 100% AD vs bvFTD: 100% bvFTD vs DLBPD: 100%
Russo et al.	1854 (only DLB): No DLB 73% Possible DLB 13% Probable DLB 13%	DLB	DLB symptoms	Cognitive test		LBCRS vs. possible DLB 0.83 LBCRS vs. probable DLB 0.83 AT-DLB vs. possible DLB Specificity: 0.72 AT-DLB vs. probable DLB 0.75	LBCRS vs. possible DLB 0.53 LBCRS vs. probable DLB 0.85 AT-DLB vs. possible DLB 0.13 AT-DLB vs. probable DLB 0.75		LBCRS vs. possible DLB 0.78 LBCRS vs. probable DLB 0.83 AT-DLB vs. possible DLB 0.72 AT-DLB vs. probable DLB 0.76

Kamohara et al.	49: 17 iNPH w/o AD/PS, 17 iNPH with AD comorbidity, 15 iNPH with PS comorbidity	iNPH iNPH/AD iNPH/PD	Cognitive deterioration in iNPH	Cognitive test		Group 1 vs. Group 2 47.1% Group 1 vs. Group 3 73.7% Group 2 vs. Group 3 60.0%	Group 1 vs. Group 2 94.1% Group 1 vs. Group 3 76.5% Group 2 vs. Group 3 88.2%	Group 1 vs. Group 2 p-value (RAVLT): p = 0.015 Group 1 vs. Group 3 p-value (Stroop test - Colour-naming): p = 0.006 Group 2 vs. Group 3 p-value (Stroop test - Colour-naming): p = 0.009	
Padovani et al.	107 MCI	AD FTD DLB	MCI	Transcranial magnetic stimulation			MCI-AD With TMS: 77.1% (95% CI [73.3–81.2]), p = 0.003 With amyloid markers: 78.9% (95% CI [73.9–84.3]), p = 0.002 With both markers: 90.0% (95% CI [86.2–94.1]) or 91.3% (95% CI [88.2–94.6]) depending on the order, p < 0.001 compared to baseline assessment or single markers MCI-FTD With TMS: 75.5% (95% CI [69.1–82.4]), p = 0.044 With amyloid markers: 75.3% (95% CI [70.3–80.7]), p = 0.028 With both markers: 88.8% (95% CI [83.2–94.8]) or 84.8% (95% CI [79.1–90.9]) depending on the order, p < 0.001 compared to baseline		

							assessment or single markers MCI-DLB With TMS: 76.9% (95% CI [68.1–86.8]), p = 0.033 With amyloid markers: 77.5% (95% CI [70.1–86.5]), p = 0.014 With both markers: 83.0% (95% CI [74.2–92.9]) or 86.7% (95% CI [75.3–99.9]) depending on the order, p < 0.001 compared to baseline assessment or single markers MCI-Other With TMS: 72.5% (95% CI [64.2–81.9]) With amyloid markers: 73.3% (95% CI [67.0–80.2]) With both markers: 85.4% (95% CI [75.6–96.4]) or 78.6% (95% CI [69.5–89.0]) depending on the order, not significantly different from baseline assessment or single markers		

Schumacher et al.	106: 39 MCI-LB, 36 MCI-AD, and 31 healthy controls	AD DLB	MCI	Cognitive / Quantitative EEG	Waveguard caps (ANT Neuro, The Netherlands) comprising 128 sintered Ag/AgCl electrodes	Delta Power: 0.89 Theta Power: 0.89 Pre-alpha Power: 0.83 Alpha Power: 0.97 Beta Power: 0.81 Theta/Alpha Ratio: 0.83 Dominant Frequency (DF), every elettroded 0.86 Dominant Frequency (DF), occipital elettrodes: 0.86	Delta Power: 0.23 Theta Power: 0.33 Pre-alpha Power: 0.56 Alpha Power: 0.41 Beta Power: 0.61 Theta/Alpha Ratio: 0.49 Dominant Frequency (DF), every elettrodes: 0.51 Dominant Frequency (DF), occipital elettrodes: 0.51		
Kozlova et al.	102: Parkinson's Disease (PD) patients: 48 No cognitive impairment: 20 Mild Cognitive Impairment (PD-MCI): 20 Dementia (PD-D): 18 Amnestic Mild Cognitive Impairment (aMCI): 15 Mild Alzheimer's Disease (mild AD): 24	AD PD	Short-term Memory	Cognitive test		Controls vs. Mild-AD: 0.96 Controls vs. aMCI: 0.87 Controls vs. PD-D:0.93 Controls vs. PD-MCI: 0.70 Mild-AD vs. PD-D: 0.88 aMCI vs. PD-MCI: 0.75	Controls vs. Mild-AD: 0.91 Controls vs. aMCI: 0.93 Controls vs. PD-D: 0.27 Controls vs. PD-MCI: 0.30 Mild-AD vs. PD-D: 0.62 aMCI vs. PD-MCI: 0.93		

Appendix B: PD vs ET Table Results

Authors	Partecipants	Diseases	Symptoms	Modal	Instrumentation (WD: Wearable Device)	Specificity	Sensitivity	p-value	Accuracy
Ratajska et al.	712: 448 PD, 128 ET, 136 HC	PD ET	Anxiety, apathy, and depressive symptoms	Cognitive and other tests					
Shahtalebi et al.	81: 47 PD, 34 ET	PD ET	Pathological hand tremor (PHT)	Movement	Inertial sensors WD: X				NeurDNet reports a maximum accuracy of 95.55% when the training/test ratio is 3:1, with 75% of the data reserved for training
Sushkova et al.	41: 20 PD, 13 ET, 8 HC	PD ET	Hand tremor	Movement EEG	Inertial sensors Electrical sensors (EEG) WD: X				The accuracy of early stage PD: 100 Accuracy PD vs ET: 90%.
Yang et al.	50: 29 PD, 5 ET, 24 HC	PD ET	Tremor	Movement	Electrical sensors				The accuracy of the GRNN classifier with PSO optimisation is mentioned as high in the learning method, with a 100% correct classification rate in the learning phase and an average hit rate of 98.93% in the recall phase in identifying the correct classes

Barrantes et al.	52: 17 PD, 16 ET, 12 HC, 7 with tremor of undecided diagnosis (TUD) (who were re-evaluated one year after the first visit to reach the definite diagnosis)	PD ET	Tremor	Movement	Inertial sensors WD: X	Part 1: Discrimination between patients with tremor and healthy subjects Specificity for Rest: 82.5%. Specificity for Posture: 91.7%. Part 2: Discrimination between PD and ET Specificity: 100% for PD Specificity: 94.1% for ET	Part 1: Discrimination between patients with tremor and healthy subjects Sensitivity for Rest: 83.3% Sensitivity per Posture: 87.5%. Part 2: Discrimination between PD and ET Sensitivity: 100% for PD (17/17) Sensitivity: 93.8% for ET (15/16)	Part 2: Discrimination between PD and ET P-value for RPC in Posture: 0.014 P-value for RE: <0.001	Part 2: Discrimination between PD and ET Accuracy for PD vs. ET: 84.38%.
di Biase et al.	58: Test group: 16 resting tremor recordings of PD patients, 20 postural tremor recordings of ET patients Validation group: 42 rest tremor recordings of PD patients, 8 postural tremor recordings of ET patients	PD ET	Tremor	Movement	Inertial sensors WD: X	ET vs PD: 88% PD vs ET: 90%	ET vs PD: 95% PD vs ET: 69%	P-values < 0.001 in both the test and validation cohorts	ET vs PD: 85% PD vs ET: 85%
Locatelli et al.	27: 16 PD, 11 ET	PD ET	Tremor	Movement	Inertial sensors WD: X				
Surangsrirat et al.	52: 32 PD, 20 ET	PD ET	Tremor	Movement	Inertial sensors WD: X				

Appendix C: PD vs PSP vs MSA Table Results

Authors	Partecipants	Diseases	Symptoms	Modal	Instrumentation (WD: Wearable Device)	Specificity	Sensitivity	p-value	Accuracy
Schröter et al.		MSA DLB PSP CBS	Disease progression, ocular motor dysfunction, gait and posture, green flags, neuropsychology, oropharyngeal impairment	Other test (Delphi method)					
Hu et al.	73: 41 MSA, 32 PD	MSA PD	Non-motor symptoms (in MSA are mainly manifested as autonomic dysfunction, such as urination disturbance, sexual dysfunction, blood pressure variation, etc.)	EMG	Electircal sensors (EMG)	Males: Specificity: BCR latency: 68.4% Mean duration EAS-EMG MUPs: 86.4% Polyphasic ratio: 59.1% Females: Specificity: BCR latency: 90% Mean duration MUPs EAS-EMG: 86.4% Polyphasic ratio: 72.7%	Males: Sensitivity: BCR latency: 89.5% Mean duration MUPs EAS-EMG: 92.3% Polyphasic ratio: 80.8% Females: Sensitivity: BCR latency: 86.7% Mean duration MUPs EAS-EMG: 90% Polyphasic ratio: 81.8%	Males: P-value: BCR latency: <0.05 Mean duration MUPs EAS-EMG: <0.05 Polyphasic ratio: <0.05 Females: P-value: BCR latency: <0.05 Mean duration MUPs EAS-EMG: <0.05 Polyphasic ratio: <0.05	Males: Accuracy: BCR latency + Average duration MUPs EAS-EMG: Sensitivity: 92.3% Specificity: 72.7%. Females: Accuracy: BCR latency + Mean duration MUPs EAS-EMG: Sensitivity: 86.7% Specificity: 90%
Leys et al.	22: 11 MSA, 11 PD	MSA PD	Cardiovascular autonomic failure	Electrophysiological test (CAFT)	Electrical sensors	100.00%	45.46%		72.73%

Zhou et al.	169: 96 PD, 33 MSA, 40 healthy controls	MSA PD	PD, MSA symptoms Ocular	Video (Video-oculography, VOG)	Optical sensors A binocular EyeLink system (Bao Runtong Research Ltd. China) was used for video-oculographic eye movement recordings	98.9% (95/96).	72.7% (24/33).		
Gandor et al.	114: 57 MSA, 57 PD	MSA PD	Laryngopharyngeal dysfunction	Video (Endoscopic evaluation (laryngeal))	Optical sensors	1	0.9		
Wu et al.	31: 21 PD, 10 MSA	MSA PD	Gait instability	Movement	Inertial sensors WD: X	89.1% ± 12.9%	89.1% ± 12.5%		89.4% ± 8.9%
Yamamoto et al.	241: 147 MSA, 94 PD	MSA PD	urinary dysfunction	Electrophysiological test	Electrical sensors	For the PVR during the free-flow study: 0.88 For the PVR during the pressure-flow study: 0.71 For the mean duration of MUPs (motor unit potentials) in sphincter EMG: 0.54	For the PVR during the free-flow study: 0.53 For the PVR during the pressure-flow study: 0.71 For the mean duration of MUPs (motor unit potentials) in sphincter EMG: 0.67	For the PVR during the free-flow study: P-value: <0.01 For the PVR during the pressure-flow study: P-value: <0.01	
Das et al.	25: 12 PSP, 13 MSA	MSA PSP	Speech disorders (3 dysarthria groups: Hypokinetic, Spastic and Ataxic)	Voice	Acoustic sensors				88%

Li et al.	25: 12 PSP, 13 MSA	MSA PSP	Speech disorders	Voice	Acoustic sensors WD: X				1D linear analysis with Factorial Discriminant Analysis (FDA): 72% FDA followed by Logistic Regression (LR): 80%
El Otmani et al.	774: 697 PD, 37 LBD, 40 PSP/CBD +100 HC	PD DLB PSP CBD	Rapid Eye Movement Sleep Behavior Disorder (RBD) Hyposmia	Other test (2 different questionnaires)		RBD: 100% Hypersmia: 90%	RBD: 76% Hypersmia: 92%		
Kowalska-Taczanowska et al.	116: 30 PD, 30 PSP, 30 MSA, 26 HC	PD PSP MSA	Speech, and voice disorders in hypokinetic, ataxic, and spastic dysarthria in PD and APS patients	Voice	Acoustic sensors				
Belic et al.	54: 14 PD, 16 PSP, 13 MSA, 11 HC	PD PSP MSA	Hand tremor	Movement	Inertial sensors WD: X				85.18%
Shill et al.	281: 76 PD, 24 PSP, 7 PSP/PD, 174 HC	PD PSP	Hyposmia	Other test (University of Pennsylvania Smell Identification Test (UPSIT))		81.4%	84.5%		
Amboni et al.	104: 83 PD, 21 PSP	PD PSP	Gait patterns	Video Movement	Optical sensors WD: X	PD vs PSP: GAIT: 73.7% COG: 88.2% Newly diagnosed PD vs early PSP: GAIT: 81.8% COG: 80.0%	PD vs PSP: GAIT: 96.5% COG: 96.4% Newly diagnosed PD vs early PSP: GAIT: 92.3% COG: 96.3%	PD vs PSP: GAIT: 0.976 COG: 1.000 Newly diagnosed PD vs early PSP: GAIT: 0.846 COG: 0.195	PD vs PSP: GAIT: 92.3% COG: 95% Newly diagnosed PD vs early PSP: GAIT: 89.2% COG: 91.9%

Appendix D: PD Table Results

Authors	Partecipants	Diseases	Symptoms	Modal	Instrumentation (WD: Wearable Device)	Specificity	Sensitivity	p-value	Accuracy
Vargese et al.	450: 260 PD, 101 DD (differential diagnoses including movement disorders other than PD as ET, AP, etc), 89 HC	PD DD	Movement Disorder (Tremor)	Movement	Inertial sensors WD: X				For the simple activity recognition task, the best DL architecture achieved an accuracy of 78.6% (ResNet). For the task reduced to the assessment steps 'drink glass' and 'point finger', accuracy was 94.6% using simple dense neural networks.
Marino et al.	77: 41 PD, 36 HC	PD	Movement Disorder (Tremor)	Movement	Inertial sensors WD: X				
Karlsson et al.	76: 38 PD, 38 HC	PD	Dysarthria	Voice		/pa/ syllables: 0.79 /ta/ syllables: 0.76 /ka/ syllables: 0.84 Prediction of reduced articulatory precision: 0.85	/pa/ syllables: 0.75 /ta/ syllables: 0.75 /ka/ syllables: 0.85 Prediction of reduced articulatory precision: 0.92		/pa/ syllables: 80% /ta/ syllables: 83% /ka/ syllables: 93% Prediction of reduced articulatory precision: 89%

Weyhenmeyer et al.	19: 9 PD, 10 HC	PD	Neuropsychological and behavior symptoms	Video Movement Electrophysiological	Optical sensors Electrical sensors		Regarding EEG and behavioral classification: The maximum sensitivity (A') for EEG during the perturbation trials is 75%, and 74% for the non-perturbation trials. The best performing behavioral classification modalities have a maximum sensitivity (A') of 80% for both perturbation and non-perturbation trials. In the case of combining EEG and behavioral data: The maximum sensitivity (A') for EEG classification for perturbation trials improves to 0.82 compared to 0.72 For non-perturbation trials, the maximum sensitivity (A') improves to 0.84 compared to 0.76 with EEG classification alone		
Ali et al.	68: 48 PD (20 training, 28 testing), 20 HC	PD	Voice impairments	Voice	Acustic sensors				Training database: 80% Testing database: 82.14%

Martinez et al.	39: 11 PD, 28 HC	PD	Gait impaiment	Movement	Electrical sensors WD: X	77.3%	47.1%		64.1%
Turner et al.	387: 253 PD, 134 HC	PD (PD-normal vs PD-pMCI)	Cognitive deficits	Cognitive					
Guan		PD	Expression disorders Hypomimia	Video	Optical				90.06%
Yuan et al.	50.318: PD (22102 + 28216)	PD	Gait Tremor disorder	Movement					

Appendix E: Other diagnoses Table Results

Authors	Partecipants	Diseases	Symptoms	Modal	Instrumentation (WD: Wearable Device)	Specificity	Sensitivity	p-value	Accuracy
Khoury et al.	165: 93 PD, 72 HC	PD (vs ALS vs HD)	Gait (Motor symptoms)	Movement	Electrical sensors		PD vs ALS: 92.86%.		PD vs ALS: 92.86%. PD vs HD: 83.33%. PD vs HC: not specified. PD vs(ALS, HD, HC): 90%.
Kwon et al.	20: 11 PD, 9 SWEDD	PD SWEDD	Tremor	Movement	Inertial sensors WD: X				
Fernandes et al.	45: 15 PD, 15 VaP, 15 HC	PD VaP	Gait disorder	Movement	Inertial sensors WD: X	Patients (IPD + VaP) vs. Controls MLP Model Specificity: Not explicitly mentioned for this comparison DBN Model Specificity: 100% (with and without MoCA) VaP vs. IPD MLP Model Specificity: Not explicitly mentioned for this comparison DBN Model Specificity: With MoCA: 73.33% Without MoCA: 66.67%	Patients (IPD + VaP) vs. Controls MLP Model Sensitivity: 93.33% (with and without MoCA) DBN Model Sensitivity: Not explicitly mentioned for this comparison VaP vs. IPD MLP Model Sensitivity: Not explicitly mentioned for this comparison DBN Model Sensitivity: With MoCA: 73.33% Without MoCA: 60.00%		Patients (IPD + VaP) vs. Controls MLP Model Accuracy: With MoCA: 95.68% Without MoCA: 94.50% DBN Model Accuracy: With MoCA: 94.17% Without MoCA: 93.50% VaP vs. IPD MLP Model Accuracy: With MoCA: 69.97% Without MoCA: 58.29% DBN Model Accuracy: With MoCA: 75.33% Without MoCA: 68.90%
Macher et al.	14: 4 anti-IgLON5, 10 PSP	anti-IgLON5 PSP	ocular motor dysfunction	Video	Optical sensors				