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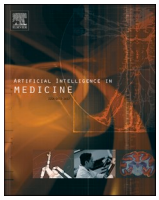

Review

Artificial intelligence in neurodegenerative diseases: A review of available tools with a focus on machine learning techniques

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ABSTRACT

Neurodegenerative diseases have shown an increasing incidence in the older population in recent years. A significant amount of research has been conducted to characterize these diseases. Computational methods, and particularly machine learning techniques, are now very useful tools in helping and improving the diagnosis as well as the disease monitoring process. In this paper, we provide an in-depth review on existing computational approaches used in the whole neurodegenerative spectrum, namely for Alzheimer's, Parkinson's, and Huntington's Diseases, Amyotrophic Lateral Sclerosis, and Multiple System Atrophy. We propose a taxonomy of the specific clinical features, and of the existing computational methods. We provide a detailed analysis of the various modalities and decision systems employed for each disease. We identify and present the sleep disorders which are present in various diseases and which represent an important asset for onset detection. We overview the existing data set resources and evaluation metrics. Finally, we identify current remaining open challenges and discuss future perspectives.

1. Introduction

Neurodegenerative diseases are a class of neurological disorders where neurons from the central nervous system die or are damaged causing severe disabilities, and eventually death. They are typically encountered in old age. However, disease onset might appear earlier. In the past years, their incidence increased significantly and it is expected that the increase will continue, as the world's population ages [1]. Neurodegenerative diseases are problematic and can become a burden since their cause is unknown and no cure has been discovered. Treatments are currently targeting the alleviation of symptoms. Due to recent advances in artificial intelligence, a significant help can come from the computational approaches targeting diagnosis and monitoring, e.g., *detection of disease onset*, *characterization of the disease*, *improvement of the differential diagnosis*, *quantification of the disease progression*, *tracking of the medication effects*. These tasks can be automated or at least improved with the help of machine learning algorithms.

Scope and target of this work. In this context, the present study proposes an in-depth, large scale, analysis of the existing artificial intelligence capabilities in support of the diagnosis and analysis of the main neurodegenerative diseases. Although a large number of neurodegenerative diseases can be defined [2], we target the ones with the highest prevalence and representative of the neurodegenerative spectrum, namely: Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Multiple System Atrophy, and Amyotrophic Lateral Sclerosis. To retrieve the existing literature, a total of 46 keywords were used, ranging from "*neurodegenerative medical devices*", "*handwriting Parkinson detection*","*Huntington disease machine learning*" to "*Alzheimer brain imaging machine learning*". These included combinations of the disease names, symptoms and analysis methods. The publications were selected based on the relevance attributed by the scholar.google search engine, focusing on the most impacting and recent publications. All articles that did not include computational methods or the target keywords were excluded. A summary of the article pool is presented in Fig. 1. Overall, we reviewed more than 450 articles. As the graph shows, there is an increasing interest for this topic, which is triggered not only by recent advances in deep learning but also by the promising results achieved so far. Other review works on specific neurodegenerative diseases or specific symptoms are also available. Our study goes beyond prior works by providing a general view of existing capabilities in the field rather than focusing on particular disease cases. For the completeness of our work, the reader is referred to existing reviews of

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the literature each time a relevant study is available.

Overview of our contributions. The main contributions of this study can be summarized with the following: (i) we provide a global review on existing computational approaches used in the whole neurodegenerative spectrum, (ii) we identify and synthesize a general taxonomy of neurodegenerative disorders, (iii) after analyzing current trends, we propose a taxonomy for computational approaches, (iv) we provide a detailed analysis of the various modalities and decision systems employed for each disease, (v) we identify and present the sleep disorders which are present in various diseases and which represent an important asset for onset detection, (vi) we identify and present the most prominent datasets available for building computational systems together with the evaluation methodologies, and finally (vii) we identify the main capabilities as well as the remaining open questions to be solved by upcoming developments.

Previous resources. Several previous reviews on similar topics have been identified. For Alzheimer's disease, the reader is referred to: Laske et al. [3] for a review on the different methods available for diagnosing AD, Cassani et al. [4] for a review on differentiating stages of AD progression using resting-state-EEG, Bhat et al. [5] presents the recent research performed on automated EEG based diagnosis of AD, Maestu et al. [6] for a review on MEG and EEG biomarkers for AD, Zhang et al. [7] for a review on methods for identifying MCI and AD, the conversion from MCI and the progression of AD, Alberdi et al. [8] for a review on methods for monitoring AD in an unobtrusive way, Pellegrini et al. [9] for a review on machine learning techniques used in neuroimaging for dementia and MCI, Davatzikos [10] for a brief overview of machine learning in neuroimaging. For Parkinson's disease, the reader is referred to: Keijsers et al. [11] for a review on the use of wearable movement sensors for PD detection and severity prediction, van Rooden et al. [12] for a review of identification of PD's subtypes via cluster analysis, Ahlrichs and Lawo [13] for a review of machine learning approaches for recognizing PD motor symptoms, Stenis et al. [14] for a review of wearable accelerometry-based technology for PD rehabilitation purposes, Pasluosta et al. [15] for a review of existing wearable technologies and the Internet-of-Things concept in support of PD diagnostics and treatment, Kubota et al. [16] for a nontechnical tutorial review of relevant machine learning algorithms for large-scale wearable sensor data in PD, Cummins et al. [17] for a review of speech analysis for health in general that includes also dysarthic PD speech, and Impedovo and Pirlo [18] for a review of dynamic handwriting analysis via pattern recognition for the assessment of neurodegenerative diseases, including PD. In contrast to previous work, apart from presenting the latest methods, we focus on a more general perspective, addressing all modalities and computational approaches in an interconnected way, while investigating the current capabilities of the algorithms. For Huntington's disease, there are currently no review publications with a specific focus on the technical aspects of diagnosis or monitoring. Several publications provide an overview of the methods available for analysis and detection of different gait abnormalities in either neurological or human movement disorders, including HD: Orru et al. [19] provides a review of the different uses of SVM for the identification of imaging biomarkers for neurological diseases in MRI, PET or DTI scans, Figueiredo et al. [20] investigates also the use of SVM, but for identifying gait patterns in human motor disorders, Moon et al. [21] provides a systematic overview of evidence for gait variability in neurodegenerative diseases such as: AD, ALS, HD and PD. For the Amyotrophic Lateral Sclerosis, there is a relative sparsity in computational methods developed and we have identified a single overview providing information on dysarthia in ALS. Tomik and Guiloff [22] analyze both clinical symptoms and the technical methods used for the differential diagnosis based on acoustic features. The current work goes beyond these aspects for a more updated and broader analysis. For Multiple System Atrophy, there are currently no prior literature reviews on the computational techniques used in its monitoring and diagnosis. This holds also for REM sleep behavior disorder where no overview articles dealing with the computational approaches are available. For restless legs syndrome and periodic limb movement, a systematic review was published by Plante [23] on the use of leg actigraphy for periodic limb movements. In contrast, the current study reviews up-to-date current technology and broader implications on the study of neurodegeneration.

Abbreviations. Throughout the entire paper we will use the following abbreviations (by alphabetic order): AD — *Alzheimer's disease*, ANN — *artificial neural network*, ALS — *amyotrophic lateral sclerosis*, AUC — *Area under the curve* B — *bradykinesia*, CNN — *convolutional neural networks*, CNS — *central nervous system*, CV — *cross-validation* D — *dyskinesia*, DBS — *deep brain stimulation*, DCNN — *deep convolutional neural networks*, DLB — *dementia with Lewy bodies*, DNN — *dynamic neural networks*, DTI — *diffusion tensor imaging*, ECG — *electrocardiogram*, EEG — *electroencephalogram*, EMG — *electromyography*, EOG — *electrooculogram*, ERP — *event related potentials*, FoG — *freezing of gait*, H&Y — *Hoehn and Yahr Scale*, HC — *healthy controls*, HD — *Huntington's disease*, HMM — *hidden Markov models*, ICA — *independent component analysis*, kNN — *k-nearest neighbors*, LASSO — *least absolute shrinkage and selection operator*, LDA — *linear discriminant analysis*, LOO — *leave one out*, LSTM — *long short term memory*, MCI — *mild cognitive impairment*, MRI — *magnetic resonance imaging*, MSA — *multiple system atrophy*, PCA — *principal component analysis*, PD — *Parkinson's disease*, PET — *positron emission tomography*, PNN — *probabilistic neural network*, PSP — *progressive supranuclear palsy*, PSG — *polysomnography*, REM — *rapid eye movement*, RBD — *REM sleep behavior disorder*, RF — *random forest*, RLS — *restless legs syndrome*, ROC — *receiver operating characteristic*, SPET — *single photon emission tomography*, SVM — *support vector machine*, SVR — *support vector regression*, T — *tremor*, UPDRS — *Unified Parkinson's Disease Rating Scale*.

The remainder of this article is organized as follows. Section 2 presents the relevant definitions and proposes a taxonomy for this review,

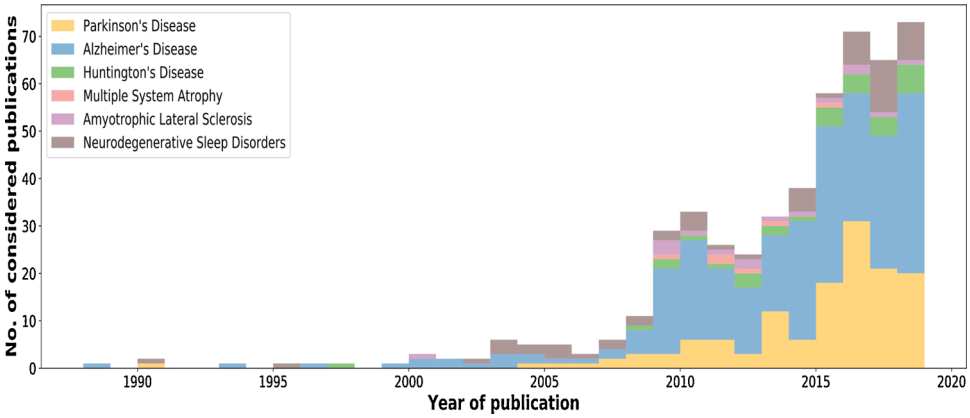

Fig. 1. Number of considered publications for this review distributed over the publication years.

from both the medical and computational point of view. Further on, each subsequent section deals with the computational approaches encountered for specific neurodegenerative diseases representating a specific category of neurodegeneration. Section 3 looks into Alzheimer's disease. Section 4 reviews Parkinson's disease. Section 5 analyses Huntington's disease. Sections 6 and 7 deal with amyotrophic lateral sclerosis and multiple system atrophy respectively. Section 8 reviews the techniques used for detecting and monitoring sleep disorders encountered in multiple neurodegenerative disorders. Section 9 provides a summary of the datasets and evaluation methods used in testing the majority of the computational approaches presented. Section 10 concludes the review and identifies gaps and future challenges for the field.

2. Definitions and taxonomy

In this section, we propose a taxonomy for the existing computational approaches for neurodegenerative diseases, both from the medical and computational perspectives. Section 2.1 defines the prominent neurodegenerative disorders along with their symptoms. Section 2.2 discusses the various theories adopted in the literature for the categorization of neurodegeneration and proposes a taxonomy. Section 2.3 defines a taxonomy for the computational approaches highlighting their purpose, the monitored disease and clinical features, along with the data modality used for analysis and diagnosis. Neurodegenerative diseases can be regarded as a class of *neurological disorders* that imply the progressive loss of neurons or subsets of neurons from specific functional-anatomical areas of the CNS [24,2]. We exclude here the neurological diseases caused by traumas at the level of the CNS. As neurodegeneration can affect many types of neurons and functional areas, their symptomatology is diverse and many different diseases can be defined. Their classification is however controversial as a significant number of symptoms overlap.

2.1. Definitions

Alzheimer's disease is a progressive age-related neurodegenerative disease characterized by the accumulation of *amyloid plaques* (beta-amyloid protein mixture), *neurofibrillary tangles* (clumps of tau proteins) and a *severe loss of connections* between neurons responsible for memory and learning [25]. Symptoms appear initially as mild memory impairments which can also be confounded with age related memory losses. These progress into severe memory impairments leading up to personality changes, language difficulties, motor difficulties, delusions and hallucinations [26]. Diagnostic criteria include the presence of AD biomarkers assessed through MRI or PET images along with an assessment of dementia symptoms and the degree of cognitive impairment [27].

Dementia with Lewy bodies is caused by the *accumulation of Lewy bodies* (clusters of alpha-synuclein protein) inside the nuclei of neurons from the cerebral cortex and basal ganglia [25]. Since both neurons involved with memory function and motor control are affected, the clinical symptoms of DLB are very similar to the dementia symptoms of AD and the abnormal movements encountered in PD.

Parkinson's disease is a motor disorder characterized by the *loss of dopamine producing neurons* through the accumulation of alpha-synuclein proteins. The main clinical characteristics include resting tremor, bradykinesia (a slowing of movements), muscle rigidity, gait and postural disturbances, sleep disorders, tiny handwriting and difficulties when speaking or swallowing [25,26]. A cure for the disease has not been discovered and current treatments focus on alleviating the symptoms, either through medication, physical therapy or deep brain stimulation. Two severity rating scales are used predominantly in medical practice: *Movement Disorder Society — Unified Parkinson's Disease Rating Scale* (MDS-UPDRS) [28] — rating based on behavior and mood, activities of daily living, motor tasks and therapy effect; *Hoehn and Yahr Scale* [29] — rating based exclusively on gait and posture impairments.

Multiple system atrophy is a progressive neurodegenerative disease that affects multiple areas of the brain and spinal cord responsible with the coordination of the autonomic nervous system [25,26]. As DLB and PD, it is also linked to the *accumulation of alpha-synuclein* but in this case in the *glia cells*. Symptoms include bradykinesia, impaired speech, orthostatic hypotension, bladder control problems, abnormal sweating and sleep disorders.

Amyotrophic lateral sclerosis is a progressive neurodegenerative disease that *affects motor neurons*. Muscles begin to atrophy as their control is no longer possible. The incipient phases of ALS usually affect the limbs and symptoms rapidly progress to other parts of the body. In the final phase of the disease, the muscles controlling the respiratory system begin to weaken. Death usually occurs within 3–5 years from disease onset due to respiratory failure. The most relevant clinical features include: severe motor impairments, muscle twitches, speech impairments, difficulties swallowing [25,26].

Huntington's disease is an inherited progressive neurodegenerative disease characterized by a *mutation in the huntingtin gene* that causes motor neurons controlling voluntary movements to die [25,2]. The symptoms include chorea (uncontrolled movements), abnormal body postures, speech impairments, changes in behavior, emotion, judgment and cognition. Death occurs in 10 to 30 years after disease onset. The diagnosis is based on genetic testing and neuroimaging techniques.

2.2. Taxonomy of neurodegenerative diseases

When placing a diagnosis, medical professionals take into account the predominant clinical symptomatology, the topography of the neurodegenerative lesion or a combination of the two. The clinical manifestations are a consequence of the specific neurons and system areas that are affected [2,30]. For instance, dementia and altered high-order brain functions are linked to the anatomical regions that include the *hippocampus*, *entorhinal cortex*, *limbic system* and *neocortical areas*. Movement disorders are associated with the damage brought to the *basal ganglia*, *thalamus*, *brainstem nuclei*, *cerebellar cortex and nuclei*, *motor cortical areas* and *lower motor neurons* of the spinal cord. At their incipient manifestation, combinations of these symptoms can be observed in several diseases [30].

It is not yet known what causes or triggers neurodegeneration, while the disease characteristics sometimes overlap and their progression is difficult to predict. In recent years, the traditional method of classifying neurodegenerative diseases based on symptomatology revealed difficulties in the diagnostic process of neurodegeneration, and as a consequence, in finding adequate treatment courses [31,2]. These difficulties stem from the extent of simultaneous occurrence of both clinical and neuropathological features defined for separate disorders in one individual at the same time. Armstrong [31] described three models to approach the classification of neurodegenerative diseases: a *discrete model*, an *overlap model* and a *continuum model*. The discrete model implies discrete diseases with little overlap of the clinical and neuropathological features. An overlap model implies a certain degree of overlay in the disease features, while in a continuum model the high degree of overlay of the features can be regarded as a continuous variation of features from one disease to another. Fig. 2 presents the overlap of four different clinical feature categories in between the selected diseases: *sleep disorders*, *cognitive* and *behavioral changes*, *speech impairments* and *motor impairments*. These can further be broken down into other specific disorders. RBD and RLS appear in diseases that seem to be characterized by alpha-synuclein depositions: DLB, PD and MSA. AD also presents symptoms related to sleep disorders, but in this case they are related to alterations in the sleep/wake cycle of the patient. Cognitive and behavioral changes as an effect of the disease are mostly encountered in dementing disorders such as AD or DLB, but also appear in HD, a disease predominantly characterized by motor dysfunctions. The most relevant cognitive impairments include memory loss and problems with

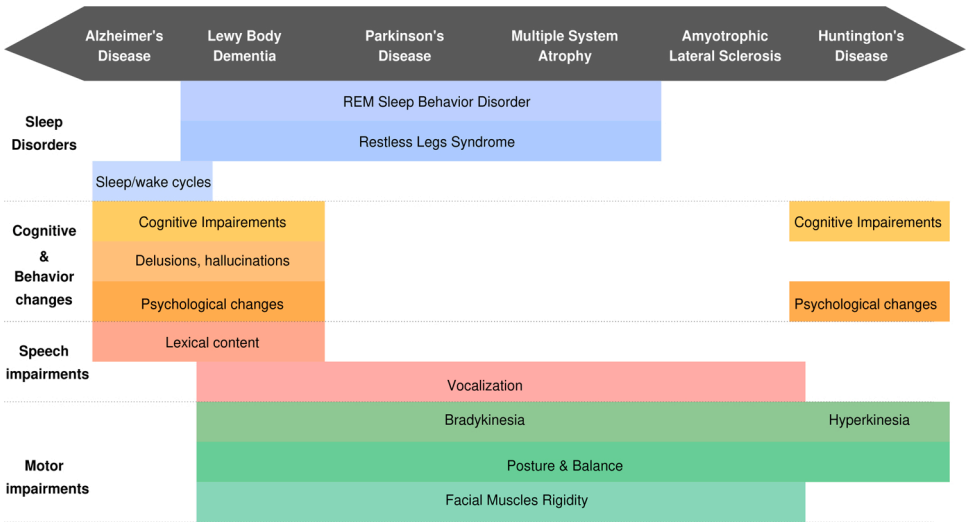

Fig. 2. Overview of the different clinical features of the most prominent neurodegenerative diseases.

perception. Psychological changes due to neurodegenerative diseases include personality changes (in AD), depression and anxiety (in DLB) and mood changes (in HD). Clinical features related to speech impairments can be regarded as modifications in the lexical content and those related to vocalization. The lexical content of speech is altered in the case of dementing diseases (AD and DLB), while vocalization is different for diseases that are governed by motor dysfunctions. Motor impairments are present in parkinsonism syndromes. Hence bradykinesia, posture and balance dysfunction along with facial muscle rigidity are clinical features of DLB, PD and MSA. HD also presents motor impairments but unlike parkinsonism diseases, it presents hyperkinesia characterized by chorea and tremor.

The nosological approach used by medical professionals to diagnose their patients involves an analysis of the main clinical symptoms along with imaging the lesions, if possible. Computational approaches can be used as an aid in the diagnosis and monitoring of these diseases by tracking different classes of symptoms. They can be used either for disease identification or for monitoring the progression and evaluating different treatment courses, either through medical follow-ups or remote tracking. Hence, *in our taxonomy we approach a classification of neurodegenerative diseases based on the clinical symptomatology*. A symptomatology which can also be tracked for following progression and for disease identification. Following the study of Kovacs [30], we propose three categorizations for neurodegenerative disorders based on their predominant clinical characteristics: *dementia*, *abnormal movements* and the *combination of the two*. The disorders characterized by abnormal movements can be further subdivided into *hypokinetic* and *hyperkinetic*. In hypokinetic diseases, movements are slowed or diminished, whereas in hyperkinetic disorders, uncontrolled movements appear. The taxonomy is provided in Table 1 (the sources for the prevalence data are the following articles [32–34] and online documents[1]). The list of diseases is not exhaustive, but provides a complete overview from the perspective of existing computational approaches. The prevalence of these disorders is increasing and it is estimated that the number of patients will double by 2050 [1], along with the increase in the older population. Details on the prevalence of each disease is available in Table 1. As neurodegeneration is a process affecting mostly individuals older than 60 years, most data is reported in literature with respect to the elder population. Significant variations are reported between different areas of the globe, with a slightly higher prevalence in low and middle income countries. Out of all neurodegenerative diseases, the dementing ones have the highest prevalence, with AD taking the leading role.

Based on the proposed taxonomy, we have selected several diseases that we considered representative for each disease category. For the dementing disorders, we have chosen to focus on Alzheimer's disease due to its slightly higher prevalence compared to other diseases in this group (0.6% see Table 1). Although fronto-temporal dementia is the second most encountered dementing disorder, we do not focus on this disorder as most of the symptoms overlap with AD. Some aspects of the differential diagnosis between AD and FTD are covered in Section 3. From the motor hypokinetic disorders, Parkinson's disease has the highest prevalence (0.2% see Table 1) and was included in this survey. Although MSA and ALS (with prevalence of 0.003% and 0.006%, respectively see Table 1) are also hypokinetic disorders, we have decided to include them in this survey due to the paucity of studies using machine learning techniques. As they present similar symptoms to PD, aspects on their differential diagnosis is also included. Huntington's disease was chosen as a representative of the motor hyperkinetic disorders group as it has the highest prevalence compared to similar diseases (0.004% see Table 1).

2.3. Taxonomy of computational approaches

Having analyzed the medical perspectives of neurodegeneration and identified the prominent diseases, we now focus on the existing computational approaches that come in support of the diagnosis, monitoring and improvement of the patient's life. As previously mentioned, we shall focus on a *symptomatology-based* analysis. Table 2 illustrates the proposed taxonomy of existing approaches. We propose a classification based on: *clinical symptomatology* and the *disease* they characterize or detect, *basic modality* used as input in the computation and *their goal*. The symptomatology is divided into five main categories: (1) *Sleep disorders* — which can be further subdivided into several disorders. REM sleep behavior disorder (RBD) and restless leg syndrome (RLS) (see Section 8). (2) *Speech impairments* — are observed in both dementing and motor debilitating neurodegenerative diseases, however their manifestation is different. In dementing disorders, the lexical content of the speech is altered. In motor disorders, the muscles controling speech production are affected and thus vocalization impairments are present. (3) *Motor impairments* — the most visible effect of

[1] https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf, https://www.alzheimer-europe.org/Dementia/Other-forms-of-dementia/Neurodegenerative-diseases, https://emedicine.medscape.com/article/1151013-overview, https://www.karger.com/Article/FullText/443738, https://www.valueinhealthjournal.com/article/S1098-3015(18)31696-6/fulltext.

Table 1
Taxonomy of nerodegenerative diseases: classification based on symptoms, specific disease examples, affected areas, prevalence (* percent normalized to 100,000 people), clinical symptoms indicative of the overlap between diseases, and prevalence of sources cited in this article.

Class		Disease	Lesion topography	Prevalence*	Main clinical symptoms	#Articles
Dementing		Alzheimer's Disease	Cerebral cortex, Hippocampus, Basal nucleus of Meynert	0.6%[2015]	Personality changes, cognitive and memory impairments, delusions, hallucinations	135
		Frontotemporal Dementia	Frontal and temporal lobes of the cerebral cortex	0.02%[2013]	Altered personality, apathy, disinhibition, impaired memory, planning, attention, perception	NA
Dementing and abnormal movements		Lewy Body Dementia	Cerebral cortex, Basal ganglia	0.002%[2016]	Cognitive impairments, delusions, depression, anxiety, rigidity, mask-like face	NA
		Corticobasal Degeneration	Cerebral cortex, Basal ganglia	0.006%[2013]	Language impairment, muscle twitches, abnormal posture	NA
Abnormal movements	Hypokinetic	Parkinson's Disease	Basal ganglia	0.2%[2017]	Slowing of voluntary movements, muscle rigidity, resting tremor, difficulty speaking, gait and postural disturbances, tiny handwriting, sleep disorders	259
		Olivoponto cerebellar atrophy	Cerebellum, Pons, Inferior olives	0.005%	Ataxia, tremor, rigidity, sleep disorders, depression, tremor	NA
		Progressive Supranuclear Palsy	Cerebral Nuclei	0.006%[2013]	Loss of balance, difficulty moving eyes, slowing of movement, slurred speech, personality changes	NA
		Multiple System Atrophy	Several areas of the brain and spinal cord	0.003%[2013]	Low blood pressure when standing up, abnormal breathing during sleep, difficulty urinating, abnormal sweating, slowness of movement, impaired speech	6
		Amyotrophic Lateral Sclerosis	Spinal cord	0.006%[2013]	Weakening of the muscles, sleep disorders, involuntary uncontrolled sighing, problems swallowing	15
	Hyperkinetic	Huntington's Disease	Basal ganglia (caudate nucleus, corpus striatum)	0.004%	Uncontrolled movements, abnormal body posture, changes in behavior and cognition	50
		Essential Tremor	Basal ganglia	0.003%	Tremor of the hand, head, arms, voice, tongue, legs	NA

Table 2
Taxonomy of computational approaches: clinical features or disease they deal with, diseases sharing these features, used sensor modalities and purpose of the approach (PD — Parkinson's disease, DLB — dementia with Lewy bodies, MSA — multiple system atrophy, AD — Alzheimer's disease, ALS — amyotrophic lateral sclerosis, HD — Huntington's disease).

Clinical feature		Disease(s)	Sensor modality	Purpose
Sleep disorders	REM sleep behavior disorder	PD, DLB, MSA	Polysomnography, actigraphy, EEG, EMG	Diagnosis
	Restless leg syndrome and periodic limb movement	PD, DLB, MSA	Polysomnography, actigraphy, EMG	Diagnosis
	Disturbed sleep/wake cycle	AD	Polysomnography, actigraphy	Progression monitoring
Speech impairments	Lexical content	AD	Voice	Diagnosis, progression monitoring
	Vocalization	AD, DLB, MSA, PD	Voice	Diagnosis, classification, progression monitoring
Motor impairments	Gait, freezing of gait, posture	PD, DLB, MSA, ALS, HD	Accelerometers, gyroscopes, force sensors, EMG, video	Diagnosis, classification, progression monitoring, disease identification
	Tremor	PD, DLB, MSA, ALS, HD	Accelerometers, gyroscopes, EMG, actigraphy	Diagnosis, classification, progression monitoring
	Facial expressions	PD, DLB, MSA	Video, EMG	Diagnosis, disease identification
	Bradykinesia	PD	Accelerometer, gyroscopes	Diagnosis, disease identification
	Handwriting	PD	Images of handwriting, writing kinematics, EMG, accelerometer	Diagnosis, disease identification
Biomarkers	Imaging	AD, DLB, PD, MSA, ALS, HD	MRI, PET, SPECT, DTI	Diagnosis, classification, progression, monitoring
	Other biomarkers	AD, DLB, PD, MSA, ALS, HD	EEG, eye movement tracking, EMG, genetic information, proteomics	Diagnosis, classification, progression, monitoring

motor impairments is the effect they have on limb muscle control. Thus problems with gait, tremor and posture are very often encountered. Other symptoms include reduced facial expressions and modifications in handwriting (see Sections 4, 5 and 7). (4) *Biomarkers* — the identification of specific protein depositions in specific anatomical locations by analyzing medical images can define disease biomarkers. Modalities such as EEG, EMG or eye movements can also be used as modalities to extract disease biomarkers.

Computational approaches can also be divided based on the disease they are applied to. Here we chose to look only at representative categories of neurodegeneration as presented in Section 2.2. AD is representative for dementing diseases. Frontotemporal dementia was not considered in this review as it is similar in symptoms to AD, while having a lower incidence rate. PD, MSA, ALS and HD are all predominantly motor disorders. Computational methods are highly dependent on the type of data used as input, especially when looking at feature extraction. The sensor modality used for characterizing a disease depends on the type of symptoms analyzed. Hence sleep disorders are usually characterized by PSG and actigraphy based recordings. Speech impairments are analyzed through voice recordings of participants performing different tasks, while motor impairments through a variety of sensors that measure movement in controlled and uncontrolled settings, e.g., accelerometers, EMG, videos. The purposes of using computational methods in helping patients suffering from neurodegenerative disorders is many fold. They can aid in the diagnostic by providing symptom characterization and help in identifying the exact disease. They can also be used for providing an objective monitoring method of disease progression. As the exact classification of neurodegenerative diseases is difficult when symptoms overlap, automatic methods of identifying small symptomatological differences are desired. A promising use of computational methods is the forecasting of events related to disease symptoms or even the identification and classification of the disease

prior to the clinical onset. The neurodegenerative process can sometimes start years before symptoms are observed.

3. Alzheimer's disease

In this section, we present a review of the most widely used computational approaches in the diagnosis and monitoring of Alzheimer's disease (reported metrics are presented in Section 9.4). Most studies included in the review focus on the differentiation between AD and healthy controls (baseline participants, usually age-matched), AD and its prodromal state mild cognitive impairment (MCI) or the differential diagnostic between AD and other forms of dementia. There is also significant interest in monitoring the disease progression by determining several levels of severity or trying to predict the conversion from MCI to AD.

3.1. Biomarkers

3.1.1. Use of brain imaging

Alzheimer's disease is linked to the accumulation of alpha-synuclein in the brain tissue. This accumulation can be tracked and studied through different neuroimaging techniques. Currently, neuroimaging methods are the most accurate option for providing an AD diagnosis while the patient is still alive. The golden standard for a precise AD diagnosis remains the autopsy. Since AD is the most prevalent type of neurodegenerative disease, its characteristics as revealed by neuroimaging have been extensively studied resulting in a high availability of large datasets. Topics addressed in literature include: (i) the detection of AD patients from HC [35–37], (ii) measuring disease severity [38], (iii) helping with the differential diagnostic from different types of dementia [39,40] and, the most addressed topic, (iv) differentiating between MCI, AD and HC along with the prediction of conversion from MCI to AD.

Detection of AD patients. Several recent studies have addressed the problem of differentiating between AD and HC by using deep learning techniques previously developed for other image processing problems. Islam and Zhang [36] compare the deep convolutional neural network Inception V5 model with the GoogleNet on MRI data from the OASIS dataset containing 100 AD patients and 300 HC. Using a 5-fold cross validation, an accuracy of 73.75% was obtained. Katako et al. [35] work on FDG-PET data from the ADNI database using an SVM classification algorithm in a 10-fold cross-validation. A sensitivity of 84% and a specificity of 95% is obtained for differentiating between AD and HC. Sarraf and Tofighi [37] use LeNet-5 resulting in an accuracy of 96.85% for AD vs. HC differentiation.

Measuring AD severity. The severity of AD can also be classified through neuroimaging data. Mahmood and Ghimire [38] use MRI data from a total of 687 AD patients from the OASIS dataset. These are classified into the following classes: no dementia, very mild AD, mild AD and moderate AD with an overall accuracy of approximately 90%.

Differential diagnostic. Differentiating between AD and Frontotemporal dementia based only on symptoms can be problematic. Davatzikos et al. [39] use voxel based and high dimensional pattern classification features extracted from grey and white matter regions of brain MRI. By using an SVM classifier with a leave-one-out cross--validation, the proposed algorithm can distinguish between AD and FTD with an accuracy of 84.3%. The difficulty in placing a correct AD diagnosis is valid also for other dementing disorders. The correlation between the golden standard test for AD diagnosis, the autopsy, and the data collected from MRI and neurophysiological tests several years prior to death, has been studied by Kautzky et al. [41]. A classification model was built on the collected data using the labels placed after autopsy. A random forest model was created in a 5-fold cross-validation scenario and resulted in an accuracy of only 62%.

Differentiating between AD and MCI. In some patients, mild cognitive impairment is a prodromal symptom of Alzheimer's disease. The differences in the brains of MCI and AD patients along with the conversion of MCI into AD has been extensively studied using brain imaging technology. Most studies make use of MRI data [42–46]. Some works study the differences between MCI and AD patients by combining multiple imaging technologies such as MRI and PET [47] or FDG-PET [48] or MRI and DTI [49]. Biomarkers for the conversion are proposed by extracting voxel-based features [42], morphometric and volumetric features [50]. Classification is performed using a variety of well-known algorithms adapted from other applications. In the early work of Plant et al. [42], brain changes appearing in MCI as predictors of AD are characterized by voxel based features. These features are used together with an SVM classifier allowing a differentiation of MCI from AD with an accuracy of 97.48%. An SVM classifier is also used by Salvatore et al. [43] to differentiate between MRI images obtained from MCI patients that converted to AD and MCI patients that did not convert. Using a nested cross-validation the accuracy was of 66%. Yan et al. [49] fuses MRI and DTI information for the differentiation between subjective cognitive decline, mild cognitive impairment and Alzheimer's disease. The result of an SVM classification is an accuracy of 98.58% for AD vs. HC, of 97.76% for MCI vs. HC and of 80.24% for subjective cognitive decline vs. MCI.

Deep neural networks have been gaining popularity in the field of imaging classification. Naturally, some of the methods have been adopted in the problem of AD vs. MCI classification based on brain imaging. Ahmed et al. [46] use a 3D convolutional autoencoder network for AD vs. MCI vs. HC classification based on anatomical features. The training set consisted of 210 patients from the ADNI dataset, while the test set was a selection of 30 patients from the CADDementia dataset. The result was a sensitivity of 100%, 80% and 47% for AD, MCI and HC classes respectively. Jabason et al. [45] have also used deep autoencoders for feature selection. With a 5-fold cross validation used on data from the ADNI dataset the accuracy, sensitivity and specificity obtained was of 98.55%, 98.79% and 99.31% respectively.

3.1.2. Use of EEG

As Alzheimer implies a severe loss of neuronal connections, changes can also be observed on the recorded EEG of AD patients. When compared to healthy controls, EEG signals recorded from AD patients show a slowing down of the characteristic EEG frequency bands and a decrease in complexity due to the diminished neuronal synchronization and of different types of oscillations [51]. Due to the non-invasive nature of the recording, EEG is a good candidate for the extraction of AD biomarkers. EEG based biomarkers have been used in literature to: (i) automatically classify AD patients and HC [51–53], (ii) to provide help in the differential diagnostic between AD and other types of dementia [54,55], (iii) to automatically distinguish between Mild-Cognitive Impairment (MCI) and different stages of AD [53,56].

Classification of AD patients. Most work conducted on the automatic detection of AD vs. HC is focused on extracting computational biomarkers based on the slowing down of EEG frequencies and the reduction in signal complexity. Trambaiolli et al. [52] takes advantage of the slowing down of EEG activity by extracting spectral and coherence features from EEG data and using them as input to an SVM classifier. Feature selection techniques are used to increase the performance on a dataset of 22AD and 12HC with a leave-one-out validation method. The classification accuracy was of 91.8%. Automated EEG based AD classification with a low-density EEG montage has been proposed by Cassani et al. [51]. Using only seven EEG channels, the data was pre-processed using ICA and wavelet decomposition for artifact removal. Several groups of features were extracted: spectral, coherence and amplitude modulation features. These were employed in a 10-fold cross validation framework for an SVM classified. The performance of the model was evaluated using accuracy, sensitivity and specificity (77.3%, 79.2%, 75.2% respectively).

Differential diagnosis. Placing a diagnosis of Alzheimer is not always easy as the symptoms most often overlap with other types of dementia. Several studies have proposed solutions for helping the differential

diagnosis. Dauwan et al. [54] use quantitative EEG features combined with clinical and neurophysiological information, visual EEG and cerebrosinal fluid diagnostic information for creating a model that differentiates between DLB and AD. The proposed model uses a random forest classifier and was tested on 66DLB, 66AD and 66HC subjects. An accuracy of 87% was obtained for the differential diagnostic problem. The differentiation between PD related dementias and AD is studied by Jeong et al. [55] using an LDA classifier on features extracted from wavelet energy and coherence. The differentiation between conditions was obtained with an accuracy of 79.18% revealing significant differences in the beta and gamma bands.

Differentiating MCI from AD. The majority of studies extracting AD biomarkers from EEG, use resting-state EEG recordings of different lengths. Mamani et al. [53] proposed an event related potential (ERP) based study using an N-back memory task for obtaining AD and MCI biomarkers. A statistical analysis showed a significant difference between AD, MCI and HC on EEG channels recorded over the fronto-centro-parietal part. The problem of classifying HC, MCI and AD subjects has been addressed by McBride et al. [56] based on Sugihara causality. The three class problem has been solved using an SVM classifier in a leave-one-out scenario using a small database of 15HC, 16MCI and 17AD. The best accuracy was of 95.8%.

3.2. Speech analysis

The effects of Alzheimer's related dementia can also be observed in the speech of patients. Unlike in the case of Parkinson's, where muscles controlling the production of speech are affected, Alzheimer's disease affects the content of the speech of AD patients. The majority of studies analyzing the speech of AD patients focus on features related to the semantics of the spoken communication. Topics of interest include: (i) the automatic differentiation between AD and HC [57–59], and (ii) the detection of the prodromal stage of MCI and its different intermediate stages [60,61].

Differentiating between AD and HC. A method for the automatic detection of AD subjects using the semantic content of speech was proposed by Fraser et al. [58]. A total of 370 features were extracted from the DementiaBank database using as input the syntactic complexity, the grammatical constituents, the psycholinguistics (frequency of certain words), vocabulary richness and repetitiveness but also features derived from the acoustic properties of speech. By using a multi-linear regression in a 10 fold cross-validation scenario a maximum average accuracy of 81.92% was obtained. König et al. [57] looked at semantic fluency in 93 AD and MCI patients vs. 24 HC using an SVM classifier with a leave-one-out approach. The result was an accuracy of 93.9%. López-de Ipiña et al. [62] aimed at extracting biomarkers of AD from speech, both from spontaneous speech as well as analyzing the emotional response from acoustic features. The best classification accuracy was of a 97.7% using an SVM classifier that had as input emotional features as well.

Detection of prodromal AD from MCI. Automatically identifying patients suffering from mild cognitive impairments can be useful for the prediction of conversion to AD. In this case the semantic features of speech can also be of help. In the work of König et al. [60], the distinction between MCI, AD and HC is studied through the extraction of semantic, vocal and statistical features from a short vocal task. Using random sub-sampling for data balancing and an SVM classifier, HC are distinguished from MCI subjects with 79% accuracy. Satt et al. [63] employs data regularization techniques to overcome data sparseness from a small database of 15HC, 23MCI and 26 AD subjects. Semantic, vocal and acoustic features are used with a Naive Bayes classifier. The differentiation between MCI and HC reaches an accuracy of 80% while MCI and AD reaches 87%.

3.3. Eye movement analysis

Detecting patients in the mild cognitive impairment state that could convert to AD is useful for early treatment intervention and better disease management. Existing methods make use of the different eye movement patterns resulting as a reaction to different visual stimuli. Pavisics et al. [64] use eye tracking related features, e.g., number of saccades, wave jerks, maximum fixation duration, to distinguish between AD and HC. By employing a Hidden Markov Model an accuracy of 95% is obtained. Eye tracking was also used by Parsons et al. [65] to distinguish between AD and posterior cortical atrophy. Using a Hidden Markov Model (HMM) to model movements in gaze location, a differentiation accuracy of 95.5% is obtained. Alzheimer's disease leads to severe cognitive impairments and the emotional toll it takes on the patients should not be ignored when proposing different treatment courses. Chung et al. [66] analyzes visual scanning behavior to automatically detect apathy in AD patients. Two separate LSTM cells are used to model visual scanning behavior during emotional and non-emotional stimuli presentation. The output of the recursive neural network is fed into a logistic regression classifier with an outcome of 74% AUROC within a hold out validation.

3.4. Gene analysis

The development of Alzheimer's disease in some individuals has also been linked to a certain genetic predisposition. The human genome contains a high amount of data unique for each individual. Computational methods, more specifically machine learning tools, have proved to be extremely useful in mapping this information and determining specific genetic links to diseases. AD is no exception and several works focus on identifying genes or gene interactions related to AD development. For instance, Park et al. [67] studied the genetic interactions that could be correlated to AD. The input data was fed into a Random Forest classifier to detect HC and AD related information. An accuracy of 90.2% was obtained. Huang et al. [68] aimed at identifying genes highly correlated to Alzheimer's disease from the whole genome. Genes were labeled as AD and non-AD related. By extracting several genome related features, an SVM classifier with a radial basis kernel was used. The receiver operating characteristic was of 84.56%. Xu et al. [69] also uses protein sequence information with an SVM classifier, resulting in an accuracy of 85.7% in predicting AD.

3.5. Multimodal features

Alzheimer's disease, along with all the other neurodegenerative diseases, is a complex disorder that affects many facets of the normal functioning of a patient. Using one type of modality as input for analyzing the disease might in some cases be sufficient but in most cases is not enough for an adequate diagnosis. Therefore, some researchers focused on harvesting information from complementary sources. For instance, Alvarez et al. [70] proposed the ICT4LIFE platform to monitor the behavior of AD. For a more accurate disease classification, information is obtained from multiple sources including electronic health records, body sensors and Kinect sensors. Several features are extracted and a sparse autoencoder is used for optimizing feature selection. The result is classified with a logistic regression with an accuracy, precision and recall of 98.4%, 98.7% and 98.3% respectively. Colloby et al. [71] used a combination between EEG and MRI data to distinguish between AD and DLB. Using a SVM classifier, it achieves an accuracy of 90%. The fusion of different technologies has also been investigated in this case. Fraser et al. [72] combined eye movement analysis with speech features in a logistic regression model. Using the two types of features an accuracy of 86% was obtained for classifying MCI and HC subjects. Grassi et al. [73] looks at the conversion of MCI to AD within a 3 year time frame using sociodemographic characteristics, clinical and neurophysiological test scores. With a SVM classifier, an AUC of 0.962 is obtained.

3.6. Summary

Alzheimer's disease symptoms and progression can be investigated and tracked through diverse methods. In this section, we have covered some of the topics that use computational methods in the study of Alzheimer's disease. With specific regard to machine learning techniques, these can be applied on problems with a diverse scope, ranging from AD detection to differential diagnosis and predicting disease progression. A selection of some of the most relevant machine learning research works on AD presented in this review is summarized in Table 3. The information contains details on the purpose of the study, the sensor modality, the type of classifier used and the best performance obtained.

4. Parkinson's diseases

Parkinson's disease is the second most encountered neurodegenerative disease and we consider it to be representative for hypokinetic diseases with similar symptoms. PD and other hypokinetic diseases are characterized by *bradykinesia*, *muscle rigidity* and *freezing of movements*. As the disease progresses, different impairments related to difficulties in *muscle control* can be seen in patients. Most computational methods focus on, either detecting PD vs. healthy control subjects, or on mapping the differently computed features to diseases measurement severity scales, such as UPDRS or H&Y. PD subtype classification is also of interest.

4.1. Motor symptoms monitoring

The most predominant symptoms that affect PD patients are the *motor disabilities*. Depending on the symptoms monitored and the final goal of the research, different recording and processing methodologies are used. As motor symptoms are some of the most encountered problems in PD, an abundance of studies are available on the topic. Computational methods developed for the analysis of PD motor symptoms aim at discriminating between PD and HC [74] but also at objectively quantifying the severity of the disease though comparisons to the UPDRS and H&Y scales [75–77]. Another application is the monitoring of the on/off medication states of patients [78]. Analyzing the severity of motor disability with respect to the time passed from the last medication intake, one can suggest adjustments to the treatment scheme.

Table 3
Overview of the most relevant research works using machine learning in handling Alzheimer's disease that were presented in this work. Brief details are provided on the dataset size and content, classification techniques and evaluation methods.

Purpose	Modality	Dataset	Classifier	Eval	Acc	Ref.
AD vs. HC	MRI	100AD, 300HC	InceptionV5, GoogleNet	5fold CV	73.75%	[36]
AD vs. HC	MRI	28AD, 15HC	LeNet-5	Hold out	96.85%	[37]
AD vs. HC	Eye tracking	26AD, 21HC	HMM	CV	95.5%	[65]
AD vs. HC	EEG	22AD, 12HC	SVM	LOO	91.8%	[52]
AD vs. HC MCI vs. HC	MRI, DTI	28AD, 45MCI, 38AD	SVM	CV	98.58% 97.76%	[49]
AD vs. MCI	EEG	17AD, 16MCI	SVM	LOO	95.8%	[56]
AD vs. MCI	Speech	26AD, 23MCI	SVM	LOO	93.9%	[57]
preAD vs. MCI	Speech	26AD, 23MCI	Naive Bayes	–	80%	[63]
MCI vs. HC	Eye tracking, speech	27MCI, 30HC	Logistic regression	LOO	86%	[72]
AD vs. DLB	EEG	66AD, 66DLB	RF	–	87%	[54]
AD vs. DLB	EEG, MRI	30AD, 21DLB	SVM	–	90%	[71]
AD vs. FTD	MRI	37AD, 12FTD	SVM	LOO	84.3%	[39]

4.1.1. Gait and posture

Most studies looking at the gait and posture of PD patients focus on distinguishing or characterizing different signals collected for patients with respect to HC.

Recording methods. The dynamics of gait are, in the majority of cases, characterized using wearable *accelerometer sensors* placed at different locations on the body, e.g., ankles [79], waist, wrist [80]. In this type of analysis, video recordings annotated by specialists are considered the golden standard [80]. Another approach for monitoring problems with gait is through *force sensors* placed under the foot [76,74]. This technology is particularly advantageous as sensors can easily be placed inside the shoe with no significant inconvenience to the user. EMG signals can also be used for abnormal gait detection, however these are more cumbersome to record and integrate in wearable technologies. Kugler et al. [81] used EMG sensors on the lower limb muscles for proposing objective measures of evaluating gait in standard tests. Impaired balance is also studied, for instance Stack et al. [80] use inertial sensors. Protocols for recording involve mostly walking for a specific distance or standard gait tests used by medical professionals.

Classification techniques. Most analysis performed focus on extracting time and frequency domain features for disease state classification. Statistical, entropy and energy features are predominantly extracted from the time domain signals. In the frequency domain, the predominant frequency is characterized along with the phase and the energy content. Asuroglu et al. [76] introduce a locally weighted Random Forest classification for estimating the severity of PD in comparison to the UPDRS scale, using eight force sensors. Alam et al. [74] add swing and stride time along with statistical time domain features as input to an SVM cubic kernel classifier which distinguishes between PD and HC with an accuracy of 93.6%. Three different studies amounting a total of 93 PD and 73 HC subjects with ground reaction force recordings [82] were used by Zhao et al. [83] for implementing a two-channel model combining LSTM and CNN.

4.1.2. Bradykinesia

Studies focusing exclusively on the analysis of bradykinesia in PD patients *estimate the severity of the symptoms* based on accelerometer and gyroscope sensors placed on different locations of the body [84,85]. For instance, Martinez-Manzanera et al. [85] use a Shimmer platform containing accelerometers, gyroscopes and magnetic sensors to record data from 25 PD and 10 HC subjects while performing a series of standardized motor tasks. The obtained signals were fused and features were computed both in time and frequency domain. After applying a *t*-test based forward selection wrapper for feature reduction, the remaining features were fed into an SVM classifier. The best results were obtained using a combination of seven features and resulted in error rates as low as 9.3–9.8%. Samà et al. [84] use a support vector regression for classifying symptom severity for a smaller database containing 12 PD patients with an accuracy for bradykinesia detection of 90%.

4.1.3. Freezing of gait

Akinesia occurs in some PD patients with a frequency dependent on the severity of the disease. It is possible to provide support to those suffering from a freezing of gait episode to surpass the moment [86]. Hence many studies focus on the detection of such episodes. For rehabilitation purposes, the detection should provide good performance in uncontrolled environments with as little intrusion as possible. Most of the studies focus on the detection of freezing of gait episodes using *inertial sensor* based wearable technologies. These include accelerometers

and gyroscopes [87] placed on the waist [88], thigh [86] or wrist [89]. Gait specific features are extracted from the time domain, e.g., statistical measures [89,90], step and stride time and length [91], and frequency domain, e.g., freezing index [86], power in different frequency bands [89]. Good results were obtained in several studies using the SVM classifier [88,91]. Deep learning models are also investigated. Camps et al. [87] used a six layer convolutional network for FoG detection on 21 PD patients. The deep learning framework achieved 90% for the geometric mean between sensitivity and specificity. Since smartphones already incorporate these recording modalities and are ubiquitously available, their performance in this circumstance has also been evaluated by some studies [90]. EEG signals have also been used by Handojoseno et al. [92] for FoG onset detection. Their dynamics were analyzed with wavelet transform based entropy measures and a back propagation neural network classification.

4.1.4. Tremor

A characterization of disease severity or of treatment efficiency can also be provided by the assessment of tremor severity. A convenient method of assessing tremor is through the analysis of signals obtained from accelerometers incorporated in wearable technology. Rigas et al. [93] propose the use of Hidden Markov Models on accelerometer signals obtained from different parts of the body of 18 PD and 5 HC subjects in different resting conditions. Tremor severity was assessed with an accuracy of 87%. Kostikis et al. [94] use a smartphone for training machine learning algorithms to distinguish the severity of parkinsonian tremor on a database of 25 PD and 20 HC participants. A bagged ensemble of decision trees provided the best results with 82% of the patients being classified correctly.

4.1.5. Dyskinesia

A side-effect of levodopa medication used for alleviating PD symptoms is the appearance of uncontrolled movements. The severity of the unwanted effects of medication can also be tracked. Chelar et al. [95] use magnetic motion trackers to quantify the complexity of involuntary movements present in 10 dyskinetic PD, 10 non-diskinetic PD and 10 HC participants with the help of multiscale entropy. Automatic recognition of dyskinetic episodes was performed using multilayer perceptrons. Inertial sensors are a more natural choice for dyskinesia assessment. Tsipouras et al. [96] used accelerometers and gyroscopes placed at the wrists, legs, chest and waist on a similar sample size to automatically recognize dyskinetic patients using an artificial neural network with one hidden layer and time and spectral features as input. The result was an average classification accuracy of 84.3%.

4.1.6. Multiple-symptoms — "on/off" state detection

The approaches presented above tackle the detection and characterization of only one specific PD motor symptom at a time. However, patients most often experience a combination of motor symptoms at a time. Tracking a combination of the symptoms in different environments and with different medication intake can be problematic.

Controlled environment — on/off detection. For an accurate assessment of the patient's state and of the disease progression, as many motor aspects as possible should be considered in more complex systems. In the early work of Patel et al. [77], the Shimmer platform was used with accelerometers placed on both lower and upper limbs to classify the severity of tremor, bradykinesia and dyskinesia. Standardized motor tasks were performed according to the motor section of the UPDRS. A total of 31 feature combinations were extracted and fed into seven SVM classifiers with different kernels. The lowest mean estimation error was of 1.2%.

Ambulatory setting — on/off detection. Salarian et al. [97] use a miniature gyroscope placed on the upper limbs for estimating tremor and bradykinesia but this time in an ambulatory setting. The algorithm made use of spectrum analysis for tremor detection and the Hilbert transform for bradykinesia estimation. The tremor detection showed an overall sensitivity and specificity of 99.5% and 94.2% respectively. Cole et al. [98] tested several dynamical machine learning techniques. Dynamic support vector machines and Hidden Markov Models had both error rates below 10%. In general, focus is placed on the development of unobtrusive systems for monitoring in uncontrolled environments. An important achievement is the REMPARK system that was designed for long term home monitoring of PD patients. It comprises accelerometers and gyroscope sensors placed on the wrist and waist of the patients. Bayés et al. [78] validate REMPARK in detecting on-off states of 41 PD patients with 97% sensitivity and 88% specificity.

Monitoring of deep brain stimulation effects. Another lead is to estimate the effects of DBS treatments. The work of Zwartjes et al. [75] investigates the daily activities of 6 PD and 7 HC patients and extracts information for quantification of tremor and bradykinesia. After applying a Decision Trees based activity recognition algorithm, features are extracted for characterization of rest and kinetic tremor, bradykinesia and hypokinesia and threshold-based algorithms are applied. Kinetic tremor was identified with an accuracy of 78.7% during sitting and 81.7% during standing. Angeles et al. [99] evaluated rigidity, tremor and bradykinesia with the goal of DBS treatment optimization. 7 PD subjects performed specific motor tasks with 3D accelerometer, gyroscope and magnetometer sensors placed on the most affected hand. Several classification algorithms were used to achieve an average accuracy of 90.9%.

4.2. Speech monitoring

As PD causes the loss of neurons in the basal ganglia, the muscles involved in the production of speech are also affected by the same symptoms as the other motor muscles, i.e., rigidity, hypokinesia, and tremor. This causes a great majority of PD patients to have dysarthic, abnormal speech [100]. Although the difficulties in speech production can be regarded as another motor symptom, we have decided to describe the computational approaches used on abnormal PD speech separately due to the abundance of literature and the different sensor modalities that are used as input. Dysarthic speech can be characterized by several particular dysfunctions caused by the loss of proper motor control. In the case of PD these include: dysphonia, imprecise articulation, dysprosody and speech volume intensity fluctuations.

Applications. Most of the studies focus on the detection of PD patients from the general healthy population [101–104]. Other studies focus on the differential diagnosis between PD, MSA and PSP [105], on progression monitoring [106] and severity monitoring [90]. Another promissing application for speech in PD analysis is the detection of PD in an incipient stage, before a clinical diagnostic is placed [104,107]. Harel et al. [108] analyze speech of two English speaking PD patients and two age-matched healthy controls retrospectively and concluded that some of the frequency content analyzed was relevant for the early identification of PD.

Features used. When tackling dysarthic PD speech, statistical features are extracted from the time domain and specific frequency features are explored. There is a high number of proposed features as the field of general speech processing is well developed. The type of features selected depend on the type of problem studied, i.e., phonation, articulation, rhythm or volume. Time domain features include: duration of pause intervals, rate of speech timing, change in interval length, period of onset of vocalization, vowel keeping time, descripive statistical measures [109–111]. Frequency features are also diverse and some of the most relevant are: main frequency of vocal cord vibration or pitch, jitter, shimmer, noise-to-harmonics ratios, formant frequencies, vowel space area, pitch and amplitude perturbation quotient, Mel Frequency Cepstrum Coefficients [102,110–112].

Classification algorithms. For all classification problems tackling PD speech, i.e., PD vs. HC, differential diagnosis or severity monitoring, the most used classification algorithm is SVM [102,110,112]. The early work of Little et al. [102] used a SVM model with a Gaussian Radial

Basis Kernel function and resulted in an accuracy for PD identification from speech of 91.4%. Orozco et al. [110] distinguished between Spanish speaking PD patients and HC using a SVM with a soft margin and Gaussian kernel in a 10-fold cross validation strategy resulting also in a high accuracy of 91.3%. However, there are other relevant approaches. For instance, Mekyska et al. [106] use a Random Forest classifier for PD severity assessment on a database with 84 PD and 49 HC patients. A sensitivity of 92.86% was obtained. The early work of Das [113] compares Neural Networks with Decision Trees and regression algorithms. The neural network provided the best result, with an accuracy of 92.9%.

Real-life recordings. The majority of the studies looking at dysarthic PD speech focus on ideal voice recording conditions. However, PD detection algorithms should be sufficiently robust for real-life, noisy scenarios. Applications in early detection of PD would be most efficient in population screening scenarios. Vásquez-Correa et al. [103] analyze the effect of different noise conditions, e.g., saturation, dynamic compression, additive white Gaussian noise and different kinds of environmental noise. Results show that different background environmental noises have a high impact on the classification results. Another method of continuously assessing the condition of PD patients is through the use of a mobile phone, either in a test application or through recording of phone conversations or via the cellular network. Rusz et al. [111] evaluates the use of smartphone speech recordings for early PD detection. The system was tested on 50 patients suffering from RBD and promising alterations in the speech pattern of prodromal PD subjects was obtained. The distinction between HC and RBD patients was obtained with an AUC of 0.69, a sensitivity of 69.8% and a specificity of 64.7%.

4.3. Handwriting analysis

The analysis of handwriting has proven effective in the diagnosis and progression monitoring of PD patients [18]. Handwriting is a complex activity involving both cognitive and motor functions. As the disease progresses and affects the brain centers responsible for its motor aspects, several abnormal characteristics of the handwriting activity can be observed. Micrographia, a reduction in the size of written text, is very often present in patients with PD. Bradykinesia and tremor also affect the ability of controlling the motions involved in writing. Such anomalies can be monitored either through *static* and/or *dynamic* approaches.

Static approaches. Refer to the graphical feature analysis of written text. The graphical characteristics are used to analyze the extent of micrographia and the randomness of strokes generated by tremor related movements. Typical metrics include changes in size of written characters, height of loop patterns, area of text blocks, pixel density variations based on ink content [114], density and height ratios, spiral precision index [115]. Besides providing an estimate of disease severity, these types of studies also allow for longitudinal tracking of PD progression and the identification of prodromal symptoms. For instance, Zhi et al. [114] explores the potential of using static analysis on historical signature based writing samples in the study of disease progression for 10 PD patients.

Dynamic approaches. Look at the kinematics of handwriting. In this case, symptoms related to bradykinesia, tremor and rigidity are assessed by also analyzing the on-surface and in-air movements associated with writing. Dynamic methods make use of digital tablets, smart pens with axial pressure of ink and tri-axial accelerometers [116] and EMG [115]. Depending on the modality of recording, different features are extracted. Digital tablets can usually record the point of contact (x and y directions) and pressure information. Several kinematic features are extracted including: speed of writing, changes in acceleration and velocity, writing duration and length, jerk, stroke length, descriptive statistical measures [117], the rate of pressure change with respect to time [118]. Smart pens in combination with digital tablets allow for additional tracking of in-air movements [116,119]. Bradykinesia is assessed by calculating the movement time and velocity, whereas tremor by analyzing the frequency content of the pen tip trajectory during rest. The use of EMG was explored by Loconsole et al. [115] and specific signal features are extracted: root mean square, mean absolute value, zero crossings of the EMG signal.

Classification algorithms. Machine learning algorithms are used for classification of the PD or HC states. Drotár et al. [118] use SVM in several handwriting classification tasks. This classification method obtained an accuracy of 81.3% on the kinematic and pressure features database PaHaW, composed of 37 PD patients and 38 HC [118]. Loconsole et al. [115] observed that SVM outperforms artificial neural networks with and without PCA based feature reduction on a smaller EMG database. Deep learning methods were also used by Pereira et al. [116]. The authors developed a convolutional neural network for handwritten dynamics differentiation on the HandPD dataset comprised of 74 PD and 18 HC.

4.4. Face video analysis

In the process of PD neurodegeneration, neurons from the basal ganglia start dying leading to dysfunctions in the neuronal circuits controlling facial muscles. As a result, some PD patients suffer from hypomimia, a reduction in the facial muscle movements (facial bradykinesia). Hypomimia in Parkinson's disease is quite a recent research topic and efforts are being made to better characterize these movement deficits. Gunnery et al. [120] used videos of participants mentioning pleasant activities to map spontaneous facial expressions in PD. The analysis was performed by extracting facial action units and characterizing features such as onset, offset and apex. Similarly, Livingstone et al. [121] used EMG to study facial muscle reaction during presentations of calm, happy, sad, angry and fearful emotions. Hypomimia was observed with a reduction in EMG amplitudes and delayed onset in the muscles controlling smiling. The video based analysis of facial expressions in PD patients relies on the general knowledge available for video facial emotion recognition and focuses on distinguishing healthy controls from diseased individuals. Bandini et al. [122] used a Multi-class SVM to train a facial expression recognition model from benchmarked databases. The test dataset comprised videos from both PD and HC. The performance of the model is proposed as an indication of hypomimia effects.

4.5. Brain imaging

Some of the most common Parkinson's disease biomarkers are the changes observed in brain tissue through non-invasive imaging techniques. The identification and characterization of such biomarkers is important for placing an initial diagnostic and following disease progression. Perhaps the most relevant application is the use of brain imaging biomarkers for the differential diagnostic between PD and other neurodegenerative diseases with similar early symptomatology. Unlike the case of Alzheimer's disease, where brain imaging biomarkers have been extensively studied through computational approaches and specifically machine learning techniques [123], the automatic analysis of PD biomarkers is at an incipient stage.

Topics addressed. Brain imaging biomarkers are identified and characterized through the automatic analysis of MRI, SPECT or PET images with the purpose of differentiating between PD and HC [124–128], but also between PD and other neurodegenerative diseases (e.g., MSA [129,130], PSP [131]). Haller et al. [124] use MRI diffusion tensor imaging with specific features extracted for the classification of PD vs. HC. For the early stage differentiation of PD from HC, MSA and PSP, Marquand et al. [130] studied the extraction of different anatomical features from the whole brain and a subcortical motor network with its component regions.

Features. The feature extraction process focuses not only on the type of information that could result in PD biomarkers, but also on the brain location from where they are extracted [125,126]. As PD affects

different regions of the brain throughout different stages of progression, selecting the most probable brain area where the disease might manifest is relevant especially in early detection and differential diagnosis. Peng et al. [126] determined that the best classification results were obtained from the frontal, parietal, limbic and temporal lobes and the central region. With regard to the type of features, these can be voxel based morphometric features or low level features related to the volume of grey matter, white matter and cerebral spinal fluid, but also high level features that represent the structural connectivity [126]. Singh and Samavedham [128] proposed an unsupervised feature extraction method in combination with a least square SVM. PD data was distinguished from HC data with a 99% accuracy in a hold out validation procedure.

Classification algorithms. The most used algorithm for all the classification problems is SVM with different implementations [131,125, 126]. Adeli et al. [125] obtained the best performance with a LDA classifier in combination with a joint feature sample selection for PD detection on the PPMI database. Hirschauer et al. [127] build an enhanced probabilistic neural network (EPNN) with four layers for classifying PD patients with respect to HC. The use of EPNN resulted in a classification accuracy of 92%.

4.6. Multimedia approaches

The symptoms affecting PD patients can be diverse and monitoring only one of them might be insufficient for providing a good estimate of the disease progression. Using multiple modalities for assessing the patient's state could be beneficial. These can also be integrated in the day to day activities of the patient, not only to monitor the disease progress, but also the effectiveness of the treatment and adherence to medication.

Mobile applications. The HopkinsPD is an application proposed by Zhan et al. [132] that aims to remotely monitor PD symptoms through a smartphone platform. Five symptom types are analyzed: voice dysphonia, postural instability while standing up, gait — bradykinesia, reduced dexterity and rest tremor. Data is collected from the phone microphone, accelerometer sensor, push of a button and different self-evaluation questionnaires. The study was deployed worldwide through a mobile application and recorded data from 221 PD and 105 HC. An accuracy of 71% was reached. A similar approach was implemented by Neto et al. [133] by using iPhone sensor data for medication response detection. The best performing classification algorithm on the specific features extracted were tree based tests, including random forest. In the work of Adams [134], keystrokes recorded with the *App-Tappy* application were used for classifying early PD and HC. The features extracted included hold time, statistic measures, latency measures and statistics on latency. Several machine learning algorithms were tested.

Other smartphone applications focus on assessing dexterity of PD patients [135,136]. Aghanavesi et al. [136] used a smartphone to track how subjects performed tapping and spiral drawing tests. Several features were extracted and pre-processed using PCA. The best result for predicting PD symptom severity was obtained using a SVM classifier which resulted in a high correlation with the UPDRS ratings of each participant.

Speech and writing. Afonso et al. [137] have used deep learning methods for assessing PD based on voice analysis and dynamic techniques for writing assessment. A deep optimum-path forest clustering technique was used on 31 PD and 35 HC performing hand movements and drawing with a biometric pen incorporating a michrophone, finger grip, axial pressure of ink, tilt and acceleration. In the work of Vasquez-Correa et al. [138], speech, handwriting and gait signals are analyzed in a database containing 44 PD patients and 40 HC. A CNN is used for the multimodal analysis of PD patient data. The features obtained from the last hidden layer of the CNN are placed into a subject specific feature vector and fed to an SVM classifier.

4.7. Summary

An abundance of literature is available on the characterization of PD motor symptoms with computational approaches. The most focus is in the area of altered movement patterns. Speech disorders caused by PD have also been often investigated as speech is easy to record and the field of voice analysis has significant history. A summary of the most prominent works using machine learning for PD characterization presented in this literature review is available in Table 4.

5. Huntington's diseases

This section presents a review of the prominent computational approaches used in the diagnosis and monitoring of Huntington's disease. Its prevalence is significantly lower than in the case of AD and PD. As a consequence, the amount of studies conducted with the purpose of developing computational approaches for its monitoring and diagnosis is significantly smaller. The gait of HD patients is characterized by uncontrolled, hyperkinetic movements such as *chorea* and *dyskinesia*. Automatic monitoring of motor symptoms can be useful in analyzing disease progression.

5.1. Gait abnormalities

Classification of HD. The gait of HD patients presents significant differences from that of HC and these differences are still a subject of research. In the study presented by Pyo et al. [139], the step length, stride length and base support and their corresponding coefficients of variation of HD patients proved to be increased when compared to HC. Mirek et al. [140] used magnetic trackers to calculate the gait cycles. Results show the HD patients present insufficient flexion in the plantar and knee joints and excessive flexion of the hip when compared to normal gait parameters. Automated classification of HD gait signals has also been investigated. Manini et al. [141] uses inertial sensors attached to the ankles and the lumbar region to record stance and swing in 10 HD patients rated according to the UHDRS scale (Unified Huntington's Disease Rating Scale — clinical assessment of HD severity), 10 post-stroke patients and 10 HC. A HMM was trained in a supervised way to recognize the foot strike and toe off events with a delay of 20 ms.

Differential diagnosis. Mann et al. [142] also used a magnetic tracker for analyzing the motion of arms of PD and HD subjects. The movements caused by the two neurological disorders and recorded with the magnetic trackers were characterized by their amplitude, frequency, dispersion, entropy and other statistical features. By studying the subtle differences in abnormal movements, a more accurate initial diagnosis can be provided. For instance, Dinesh et al. [143] place a wearable sensor (BioStampRC) on the arms and legs of 10 PD, 10 HC and 15 HC for motion characterization in a simple walking test. The signals recorded included 3D accelerometers, ECG and EMG. The features extracted showed a good visual discrimination between the three conditions.

5.2. Speech impairments

Basal ganglia neurodegeneration leads to motor impairments which might affect the muscles involved in speech production. Different diseases might cause different types of abnormalities in muscle control and hence in the produced speech. Differentiation between HD and other neurodegenerative diseases such as PD, MSA and PSP, based on voice recordings, was proposed by Rusz et al. [144]. Repetitions of the 'pa' syllable where characterized by features representing rhythm instability and acceleration through the detection of syllable onset. The accuracy of the syllable onset detector was of 99.6% and the visual observation of the features showed discrimination power between syndromes. Novotný et al. [145] characterized PD and HD dysarthia by also looking at syllable onset in 'pa-ta-ka' repetitions using the Hilbert transform. The accuracy of PD syllable onset detection was of 90%, while for HD it was

Table 4
Overview of the most relevant research works using machine learning in handling Parkinson's disease that were presented in this work. Brief details are provided on the dataset size and content, classification techniques and evaluation methods.

Purpose	Modality	Dataset	Classifier	Eval	Acc	Ref.
PD vs. HC	Ground reaction force	29PD, 18HC	SVM	LOO	93.6%	[74]
PD vs. HC	Ground reaction force	93PD, 73HC	LSTM, CNN	Hold out	98.7%	[83]
PD vs. HC	Speech data	50PD, 50HC	SVM	10fold CV	91.3%	[110]
PD vs. HC	Handwriting dynamics	37PD, 38HC	SVM	10fold CV	81.3%	[118]
PD vs. HC	Handwriting dynamics	74PD, 18HC	CNN	Hold out	95%	[116]
PD vs. HC	MRI	518PD, 245HC	SVM	CV	99%	[128]
PD vs. HC	MRI	200PD, 375HC	EPNN	Hold out	92%	[127]
PD vs. HC	Speech data, handwritten dynamics, gait signals	44PD, 41HC	CNN, SVM	Hold out	97.6%	[138]
Symptom severity	Accelerometer	12PD	SVM	LOO	90%	[84]
Severity of tremor	Accelerometer	18PD, 5HC	HMM	LOO	82%	[93]
Detect FoG	Inertial sensors	21PD	CNN	Hold out	90%	[87]
Detect dyskinesia	Accelerometer	5HC, 14PD with D, 10PD	ANN	LOO	84.3%	[96]
Medication effect	Speech data, accelerometer, push of a button, questionnaires	221PC, 105HC	RF	10fold CV	71%	[132]

80%.

5.3. Biomarkers

5.3.1. Brain Imaging

Brain imaging is considered one of the most reliable methods used for confirming a HD diagnosis. Several works have focused on the development of (i) MRI biomarkers for the characterization of HD and their presence (ii) prior to disease onset.

Classification of HD. Rizk-Jackson et al. [146] uses a database of MRIs of 39 HD and 25 HC patients to extract region-based and voxel-based features from white and grey matter. Using an LDA classifier a balanced accuracy of 76% was obtained for differentiating HD and HC.

Pre-onset HD detection. Although HD is a genetic disease and carriers of the huntingtin gene are already aware they will develop the disease, the exact onset is not yet predictable. Several studies have tried to identify pre-HD signs through brain imaging biomarkers several years prior to disease onset. For HD carriers, an MRI scan is typically taken every 2 years. In practice, that is not always the case. Eirola et al. [147] propose an extreme learning machine with a hidden layer of 1000 neurons for predicting the onset of HD 10 years in advance. The output result showed an accuracy of 80–90% over the entire 10 year period. In the Predict-HD study, the MRI scans from a total of 95 preHD subjects and 95 HC subjects were used for predicting HD several years before onset. Information was extracted from the gray matter of several regions of interest and fed to a multivariate SVM. By selecting the region of interest, an accuracy of 83% was obtained. The performance of the classification of the preHD subjects increased as time to onset decreased. Mason et al. [148] used the Track HD consortium data with MRI scans from 19 preHD and 21 HC subjects to extract both structural and connectivity measures. Using a linear support vector machine preHD was identified 5 years prior to disease onset and a maximum accuracy of 88% was obtained. DTI was also used by Georgiou-Karistianis et al. [149] in obtaining biomarkers for the preHD vs. HC discrimination. Different tests were performed for extracting features either from the whole brain or from specific regions. A quadratic discriminant analysis showed a good discrimination power for the volumetric reduction and increased fractional anisotropy in the basal ganglia up to 15 years prior to onset.

5.3.2. EEG signal

As Huntington's disease also implies cognitive and psychological impairments, changes in the activity of the brain might also be observed in the EEG measurements. Tommaso et al. [150] analyzed recordings from 13 HD in order to extract possible EEG biomarkers. Features extracted from the Fourier transform of EEG signals were fed into an artificial neural network classifier which correctly predicted 11 out of 13 subjects as containing the HD gene. Odish et al. [151] went further to create an EEG index on 2 seconds Fourier transformed data. The proposed method was tested by selecting the adequate features through PCA and training an SVM model. The classification was tested on 26 HD gene carriers and 25 HC resulting in an accuracy of 83%.

5.4. Summary

As Huntington's disease is less prevalent in the population and has a strong genetic correlation, fewer research works investigating HD were found when compared to publications investigating AD or PD. Machine learning techniques are used in the study of HD to bring more clarity on the onset of the disease. A summary of the most prominent works presented in this work using machine learning for HD is available in Table 5.

6. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis is a severe motor neurodegenerative disease with a rapid progression and a low prevalance when compared to other neurodegenerative diseases. Studies that rely on computational approaches focus mostly on providing an aid to ALS diagnosis, most frequently looking at a better differentiation from other neurodegenerative diseases at incipient phases with predominant motor abnormalities such as PD, HD or MSA.

6.1. Gait abnormalities

Characterization of gait in neurodegenerative diseases, particularly in ALS, HD and PD, has been performed by Hausdorff et al. [152] by recording the magnitude, duration of stride-to-stride fluctuations and perturbations in the fluctuations dynamics by using force sensors placed on the feet of the subjects. The gait of ALS patients was less steady and more temporarily disorganized. No other studies using other databases (private or public) characterizing gait dynamics of ALS patients were found by the authors. Using the neurodegenerative diseases gait dynamics database, Dutta et al. [153] automatically identified the different disorders from healthy controls using several features extracted from a cross-correlogram with an Elman's recurrent neural network with one hidden layer. The result for binary classification (ALS vs. HC) was in the range of 90.6% to 97.8% average accuracy. Xia et al. [154] used the Teager Energy Operator to extract features for an SVM classifier. The proposed method resulted in an accuracy of 92.86%.

6.2. Speech impairments

The muscles involving speech production are also affected in amyotrophic lateral sclerosis. ALS speech abnormalities were investigated by Yunusova et al. [155] through features as articulatory rate, duration of speech and pauses. The aim of the study was to evaluate the effect on speech of diseases predominantly characterized by motor deficits and those with a predominant cognitive deficit. In this case,

Table 5
Overview of the most relevant research works using machine learning in handling Huntington's disease that were described in this work. Brief details are provided on the dataset size and content, classification techniques and evaluation methods.

Purpose	Modality	Dataset	Classifier	Eval	Acc	Ref.
HD vs. HC	EEG	26HD, 25HC	SVM	10fold CV	83%	[151]
HD vs. HC	MRI	39HD, 25HC	LDA	4fold CV	76%	[146]
HD onset	MRI	1370HD	ANN	Hold out	90%	[147]
HD onset	MRI	19preHD, 21HC	SVM	LOO	88%	[148]
Discriminate stance and swing	Inertial sensors	10HD, 10HC	HMM	–	20 ms error	[141]

significant statistical differences were observed between features extracted from the speech of ALS subjects when compared to the speech of fronto-temporal dementia. Wang et al. [156] investigated the possibilities of automatically detecting ALS from speech. The proposed method used both acoustic information and articulatory movement data. The movement data was recorded with electromagnetic articulograph sensors attached to the tongue and lips of the participant. Features were extracted from both signal sources and two classifiers were compared: SVM and a DNN. The SVM was able to classify ALS speech with an accuracy of 80.91% using both acoustic and movement data. The DNN resulted in 91.74% accuracy only using acoustic data in a 4-fold cross-validation scenario.

6.3. Video analysis

For the purposes of early diagnosis and tracking of ALS, Bandini et al. [157] investigated the use of kinematic features extracted from videos of the face while ALS and HC subjects were performing both speech and non-speech tasks. As ALS affects all motor neurons, the muscles of the face are also impaired. Using a logistic regression classifier, an overall accuracy of 88.9% was obtained when discriminating between ALS and HC.

6.4. Biomarkers

6.4.1. Brain imaging

It is used in ALS to investigate its causes and progression. Fekete et al. [158] used MRI brain scans from 40 ALS and 30 HC subjects to propose an ALS biomarker based on the organization of brain networks at a functional level. Features were extracted from the 0.03–0.06 Hz band using a typical image processing chain: motion correction was applied, followed by a normalization to the MNI (Montreal Neurological Institute) space and the use of masks for CSF (cerebrospinal fluid) and white matter extraction. For the classification task, an SVM with a recursive kernel elimination was used leading to an accuracy, sensitivity and specificity of 87%, 88% and 88%, respectively. A method for predicting the survival in ALS patients was proposed by van der Burgh et al. [159]. Both MRI and clinical characteristics were studied on 135 ALS patients classified as short, medium or long-term survivors. A deep neural network was used for prediction, leading to an accuracy of 84.4%.

6.4.2. EMG signal

As motor muscles are significantly affected in ALS, using non-invasive EMG measurements for ALS diagnosis could be a cost effective option for an initial diagnosis. Zhang et al. [160] investigated several statistical features extracted from the EMG of ALS patients and HC subjects. These were used with an LDA classifier. The classification provided a sensitivity of 90% and a specificity of 100% for differentiating ALS and HC subjects from EMG data.

6.5. Summary

The characterization of ALS through computational methods is limited in the available literature. The study of the disease through machine learning techniques is still at an early stage. Most research works focus on identifying ALS patients from HC. A summary of the research works using machine learning on ALS that are available in this literature review are presented in Table 6.

7. Multiple system atrophy

Multiple system atrophy is a severe neurodegenerative disease that progresses rapidly after onset. Its prevalence is small and as a consequence the number of studies using computational approaches for its characterization is small. Most of these studies focus on providing better methods of diagnosis in the incipient stages of the disease when the symptoms are confusing. MSA bares the closest resemblance to Parkinson's disease, especially the parkinsonian version of MSA (MSA-P). Computational approaches can help in its better diagnosis by analyzing imaging biomarkers, evaluating speech alterations and analysis of proteomics data.

7.1. Biomarkers

According to Duchesne et al. [129], the distinction of Parkinson's disease and parkinsonian plus syndromes presents an initial error rate of up to 35%. Brain imaging is generally useful in providing more insights into the correct diagnosis. Developing biomarkers for automatic detection has been studied by Duchesne et al. [129] on MRI data from MSA and PD patients. After image pre-processing, the tissue composition and deformations from the hind brain were evaluated for their discriminative power. A model created on these features with an SVM least square optimization algorithm provided an accuracy, specificity and sensitivity of 91%, 88% and 93% respectively. Similarly, in the study of Marquand et al. [130] the midbrain was the anatomical region with most discriminative power for the selection of nerodegenerative biomarkers. The MRI images were collected from PSP, PD and MSA patients. An SVM model was created, leading to an accuracy of 91.7% for MSA detection.

7.2. Speech impairments

Due to the degeneration of neurons in the basal ganglia, control of the muscles producing speech might be affected in MSA, particularly in the parkinsonian variant of the disease. MSA-P presents similar symptoms to PD. The study of Eun et al. [161] analyzes the differences in speech patterns between the two diseases. Subjects suffering from MSA-P showed more speech impairments than those with PD, reflected in the voice pitch, prolonged pause time and reduced speech rate. Soli-Soler et al. [162] proposed an analysis of the fundamental frequency of snoring for the identification of MSA patients. Although a slightly different approach than that of Eun et al. [161], the method analyzes the sounds produced by the same muscles affected by neurodegeneration.

7.3. Summary

Very few studies looking at MSA with computational approaches were found. Machine learning techniques are used to help in the differential diagnosis between MSA and other similar motor disorders. A summary of the studies using machine learning for MSA from this

Table 6
Overview of the most relevant research works using machine learning in handling ALS that were presented in this work. Brief details are provided on the dataset size and content, classification techniques and evaluation methods.

Purpose	Modality	Dataset	Classifier	Eval	Acc	Ref.
ALS vs. HC	Force sensors	13ALS, 16HC	RNN	Hold out	97.8%	[153]
ALS vs. HC	Force sensors	13ALS, 16HC	SVM	LOO	92.86%	[154]
ALS vs. HC	Speech data, articulatory movement data	11ALS, 11HC	DNN	LOO	91.74%	[156]
ALS vs. HC	Video data	10ALS	Regression	LOO	88.9%	[157]
ALS vs. HC	MRI	40ALS, 30HC	SVM	LOO	87%	[158]
ALS vs. HC	EMG	10ALS, 11HC	LDA	LOO	90% sensitivity	[160]
Survival of patients	MRI	135ALS	DNN	Hold out	84.4%	[159]

literature review is available in Table 7.

8. Sleep disorders present in various diseases

This section presents an overview of studies analyzing abnormal sleep behaviors manifested in several neurodegenerative diseases. More specifically, we investigate the use of computational approaches used for: REM sleep behavior disorder and Periodic Leg Movements (with or without restless legs syndrome). These symptoms are presented separately as they are present in multiple diseases characterized by alpha-synucleinopathies such as PD, MSA or DLB [163] and have similar clinical characteristics throughout all diseases. RBD and PLM have been until recently characterized as separate disorders. In recent years, the link with neurodegeneration has been firmly established. RBD is now considered as part of alpha-synucleinopathic degeneration and its appearance years prior to the disease onset is a prodromal symptom [164].

8.1. REM sleep behavior disorder

Rapid eye movement sleep behavior disorder is characterized by the enactment of dreams and unusual motor behavior during REM sleep, more precisely REM sleep without atonia (RSWA). The prevalance of RBD differs per type of neurodegenerative disorder. In MSA and DLB, more than 80% of patients develop RBD. For PD, the number of patients who present RBD symptoms is lower. Computational methods are used both for the characterization of RBD from polysomnographic recordings but also for the automatic detection of the abnormal recordings related to RBD.

Characterization of RBD. In recent years, changes in EEG activity in individuals with RBD have been identified. Brazete et al. [165] have showed that RBD is linked to a slowing down of EEG activity during wakefulness, with delta and theta bands presenting higher spectral powers in RBD patients vs. HC. Ruffini et al. [166] also investigated EEG complexity during awake EEG recordings using Lempel-Ziv-Welch Compression Spectrograms and entropy measures. RBD is present in the prodromal phases of multiple neurodegenerative diseases. Berrada et al. [167] attempted to differentiate between RBD patients who later on develop DLB and patients who develop PD from polysomnographic recordings and data extracted from clinical, neurological and neurophysiological exams. By applying an alternating decision tree, the algorithm was able to automatically differentiate only between RBD and HC subjects, with no significant results on the DLB or PD conversion.

Table 7
Overview of the most relevant research works using machine learning in handling ALS. Brief details are provided on the dataset size and content, classification techniques and evaluation methods.

Purpose	Modality	Dataset	Classifier	Eval	Acc	Ref.
MSA vs. PD	MRI	16PSP or MSA, 16PD	SVM	LOO	91%	[129]
MSA vs. PD, PSP	MRI	12PSP, 14PD, 19MSA	SVM	LOO	91.7%	[130]

Automatic detection. The automatic detection of RBD patients from HC subjects is of interest for the reduction in time required for placing a diagnostic. Several threshold EMG based methods have been proposed [168,169]. Cesari et al. [169] compare several available threshold-based methods. The Frandsen Index method outperformed the others with average sensitivity values of 90% for RBD patient detection. Kempfner et al. [170] proposed an RBD detection method based on the entire polysomnographic recording. Subject specific features were extracted from all signals and were used as input to an SVM classifier. The area under the curve in a leave-one-out testing scenario was of 0.988 when using all signals and 0.981 when using only EMG activity. Ruffini et al. [171] proposed an automatic detection method for RBD based on awake EEG recordings. Two classification algorithms were proposed and compared: a DCNN with a 5-layer architecture and a Recurrent Neural Network with three stacked LSTM cells. The DCNN provided the best results with a classification accuracy of 80% between RBD patients and HC in a leave-one-out validation scenario.

8.2. Restless legs syndrome and periodic limb movement

Periodic limb movements appear in patients with and without restless leg syndrome and are characterized by uncontrolled limb movements that occur during sleep [172]. RLS and PLM are present in movement related neurodegenerative disorders. The highest prevalence is in PD patients. Due to a paucity of studies, it is difficult to establish the prevalence of these movement disorders in other neurodegenerative diseases. Their presence has been observed also in MSA, PSP and HD [172]. Similar to RBD, the majority of studies including computational methods focus on the characterization of RLS and PLM or on their automatic detection either from polysomnographic or actigraphy recordings.

Characterization. The characterization of PLM through EMG recordings during sleep is still a topic of investigation. Different states of RLS and PLM were investigated by Ferri et al. [173] by introducing a periodicity index and using Markov chains for the characterization of the structure of leg movement sequences. Ferrillo et al. [174] investigated the awakenings and EEG arousal prior and after PLM events. By analyzing the content of EEG signals through the wavelet transform and extracting the heart rate from cardiac signals, a significant increase in the heart rate and delta activity power was observed 3–4 s prior to PLM onset. Similarly, Sieminski et al. [175] looked at the spectral powers of the alpha, beta and delta bands of the EEG and found an arousal after PLM activity was detected.

Automatic detection. The automatic detection of PLM events could reduce the time required for manual polysomnographic annotations. Tkach et al. [176] investigated the stability of time-domain features extracted from EMGs recorded from several muscles during PLM for their automatic detection. Using several statistical features and a linear discriminant analysis classifier, an improvement of 16% was obtained by feature and recording site selection. On the other side, Umut and Çentik [177] investigated the automatic detection of PLM using all PSG signals except EMG. A combination of Haar wavelet decomposition and Discrete Fourier Transform was used to extract the power from the delta, theta, alpha and beta EEG frequency bands. A kNN classifier used in a

10-fold cross validation scheme provided the highest accuracy of 91.87% for the detection of PLM events. The use of limb actigraphy might be a good alternative to PSG for classifying sleep disorders. Several commercial actigraphy devices are already available and have been tested for their utility in PLM detection. These include PAM-RL [178], the CE marked actigraphy device KickStrip [179] and Respironics Actigraphy [180].

8.3. Summary

Most literature available for sleep disorders related to neurodegeneration, such as PLM or RBD, propose different methods for their characterization. A few studies use machine learning for their automatic detection from regular sleep or for differentiating patients from HC. The studies presented in this literature review using machine learning for sleep disorders are summarized in Table 8.

9. Overview of the common processing steps

After reviewing the relevant literature for the various neurodegenerative disseases, in this section, we identify and analyze the common processing steps employed by the computational algorithms and machine learning techniques. These are depicted in Fig. 3. We propose a view that divides the classification process into six blocks. Neurodegenerative diseases and their symptoms are diverse and so the types of datasets available for different classification problems are varied. However, regardless of the data types, similar steps follow in case of classification problems. The raw data can be directly fed into the classification algorithm or several pre-processing steps are applied prior to classification. In some cases, the data might be pre-processed which can imply filtering, normalization or dimensionality reduction. For some studies, different types of features are extracted and further selected based on specific relevance measures. Regardless of the type of pre-processing applied, a classification algorithm is applied and the result is evaluated.

We detail these aspects in the following: a summary of the datasets available for training computational methods (see Section 9.1), an overview of the pre-processing, feature extraction and feature selection methods (see section 9.2), an analysis of the classification algorithms (see section 9.3) and evaluation methods (see section 9.4 found in this literature review.

9.1. Datasets

The spectrum of neurodegenerative disorders affects patients in different ways resulting in a variety of symptoms. The type of signals, protocols and information required to accurately diagnose or monitor these diseases are diverse. Therefore the datasets found in the literature proposing computational approaches show a mixture of recorded data, protocol for recording and size. The chosen protocol depends on the end goal of the study, e.g., to aid in the diagnosis of the disease, to monitor progression, to help in the differential diagnosis, to detect prodromal stages of the disease etc. Most of the times, the data collected is disease specific and cannot be used for other diseases as it was not collected with a protocol developed for that purpose.

A high number of studies record specific datasets for their chosen topic of study such as a small variation in symptoms or different sensor recording modalities. Therefore the amount of data collected is most of the times small, from a few participants. The majority of the datasets used are small (67.5 %), with less than 50 participants per class. These datasets tend to be private and target specific diseases or symptoms. Medium sized datasets (between 50 and 100 participants per class) make up 14.41% of the datasets considered in this study and large datasets (with more than 100 participants per class) make up 18.07%. Large and medium size datasets are predominant in all diseases in topics such as Speech processing, Brain Image analysis, Classification of Tests and Medical Records or Genetic information. Big sized datasets are generally collected in consortium or projects spanning multiple years. The majority of large datasets are made available to the research community free of charge creating the opportunity for more researchers to work on the development of adequate solutions. In Table 9, an overview of the most relevant datasets is provided along with details on their content, availability and size.

Table 8
Overview of the most relevant research works using machine learning in handling sleep disorders associated to neurodegenerative diseases. Brief details are provided on the dataset size and content, classification techniques and evaluation methods.

Purpose	Modality	Dataset	Classifier	Eval	Acc	Ref.
RBD vs. HC	PSG	16RBD, 16HC	SVM	LOO	AUC 0.988	[170]
RBD vs. HC	EEG	121RBD, 91HC	DCNN	LOO	80%	[171]
Detect PLM	PSG	153PLM	kNN	10fold CV	91.87%	[177]

9.2. Pre-processing, feature extraction and selection

In some of the studies, when predicting a certain condition or using computational approaches for placing a diagnostic, features are extracted from the raw data recorded and fed into a classification algorithm. These features are diverse and are strongly dependent on the type of input data. Prior to using features as input to a classifier, it might be useful to select relevant features or to project these into a more representative space while reducing the dataset dimensions.

When looking at feature selection, most of the studies make use of statistical measures for eliminating correlated features which add no or little additional information to the dataset. Statistical methods include computing correlation coefficients, *t*-tests, Whitney *U*-tests, Kruskal Wallis tests or mutual information [61] [194]. Other methods are based on entropy or information gain [195].

More complex feature selection techniques such as forward feature selection are also used. This technique adds features one by one as input to the classifier and selects the ones that improve the classification performance [74][196]. It is not recommended for high volume datasets. Other methods for feature selection use regression techniques such as LASSO (least absolute shrinkage and selection operator) or the feature importance computed using the Random Forest algorithm [112]. Tsanas et al. [112] also uses the RELIEF feature selection algorithm that also considers the interaction between the different features.

Dimensionality reduction is also employed in some of the studies as a pre-processing step. The most popular methods are factor analysis [58], principal component analysis [129,151], independent component analysis [197] and autoencoders [70,45]. Besides reducing the dimension of the input data set, the information is projected in different dimensions that might enhance the classification performance.

9.3. Classification algorithms

The problems approached can be binary, such as looking at whether a disease is present or not, or divided into multiple classes, when differentiating between different diseases or different stages of progression of a disease. The methods used for classifying the targeted states can be as simple as using threshold-based algorithms or imply the use of advanced machine learning methods.

Out of the studies considered in this review approximately 64% use machine learning algorithms. Fig. 4 provides an overview of the types of algorithms used in classification problems. A typical processing chain involves the pre-processing of raw signals followed by feature extraction and classification. Most proposed methods make use of supervised learning techniques where a labeled training set is presented to the

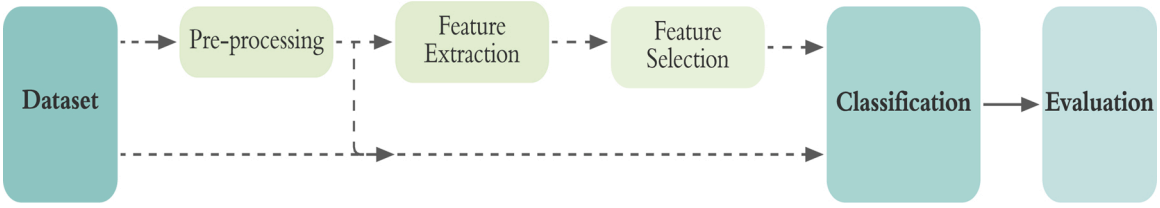

Fig. 3. Overview of the general steps used in different classification problems for neurodgenerative diseases.

Table 9
Selection of the most relevant datasets found in literature.

Name	Disease	Year	Avail.	Purpose	Data type	Size
ADNI [181]	AD	2004–2016	Open	Detection of AD and pre-AD; monitoring of progression	clinical, genetic, MRI, PET, biomarkers	ADNI1 — 200 HC, 400 MCI, 200 AD; ADNI-GO — 200 early MCI; ADNI2 — 150 HC, 100 early MCI, 100 late MCI, 150 late mild MCI, 150 AD; ADNI3 — 133 HC
AZTIAHO [62]	AD	2013	Closed	Speech biomarkers for AD	Speech data	50 HC, 20 AD
CADDementia [182]	AD	2015	Open	Detection of HC, MCI and AD	MRI data	384 Recordings
Daphnet [86]	PD	2008	Open	Freezing of gait	Accelerometer data	10 subjects
DementiaBank [183]	AD	1987–2019	Open	Speech biomarkers of dementia	Speech data	167 AD and 97 HC
Gait in Neurodegenerative Disease [82]	PD, HD, ALS	2000	Open	Gait dynamics and response to medication	Force sensor recordings	15 PD, 20 HD, 13 ALS, and 16 HC
Gait in Aging and Disease [82]	PD	1997	Open	Gait in PD	Force sensor recordings	5 PD, 5 old, and 5 HC
Gait in Parkinson's Disease [184]	PD	2005	Open	Gait in PD	Force sensor recordings	93 PD, 73 HC
Oxford PD Detection [102]	PD	2009	Open	dysphonia in PD	Speech data	23 PD, 8 HC
OASIS [185]	AD	2007–2010	Open	Detection of AD	MRI, PET	OASIS1, 416, ASIS2, 150, and OASIS3, 1098 subjects
PaHaW [186]	PD	2016	Open	Archiedian spiral drawings and handwriting for PD	Pressure, *xy*-coordinates, tilt, elevation, and in-air/on-air surface status	37 PD, 38 HC
PC-GITA [101]	PD	2014	Closed	Speech in PD	Speech data	50 PD, 50 HC
PD Speech [187]	PD	2014	Open	Speech in PD	Speech data	20 PD, 20 HC
PD spiral drawings [188]	PD	2013	Open	Drawings in PD	Digital tablet parameters	62 PD, 15 HC
PDMultiMC [189]	PD	2017	Closed	Handwriting, speech and eye movements in PD	Speech, digital tablet parameters	16 PD, 16 HC
PPMI [190]	PD	2002	Open	Biomarkers for PD	Brain images, clinical data, biological samples	432 PD, 196 HC, 64 early-PD, 65 RBD
Predict HD [191]	HD	2008	Closed	HD detection correlated to genetic data	Genetic data, cognitive assessment, tapping test, verbal learning/memory task, odour recognition, MRI	438 pre-HD
Track HD [192]	HD	2008–2014	Closed	HD detection correlated to genetic data	Genetic data, MRI, clinical, cognitive, quantitative motor, oculomotor and neuropsychiatric assessments	366 participants
Tickle-Degen [193]	PD	2010	Closed	Quality of life in PD	Video recordings	117 PD

classifier for building a model. Such techniques include linear regression, Naive Bayes, SVM, k-NN, random forests, decision trees, LDA. By far the most used classifier in all researched diseases is SVM. The popularity of SVM can also be explained by the problems tackled: a big majority of the studies look at identifying between patients and healthy controls and so handling binary classification problems. Shallow and deep neural networks have also been used, but they are not as popular as the more conventional algorithms enumerated before. Some studies use different combinations and variations of MLP, CNN, DNN, ANN. Other types of classification algorithms look into more elaborated network architectures such as EasyMKLFS, Extreme Learning, Probabilistic Neural Networks, Gaussian Neural Networks and Deep Belief Networks. Unsupervised learning was also attempted in more recent years via autoencoder networks. Deep neural networks have been more commonly used in studies using images as input for analysis, and are gaining more and more traction nowadays.

9.4. Evaluation metrics

We overview the common practices for assessing the performance of the computational systems. This brings into discussion the way the data is used for training the systems and the metrics employed for assessing the actual performance.

9.4.1. Data splitting

Although the commonly employed practices for training and validating the systems are the ones used in machine learning, there are some adaptations to the specificity of the data. We overview here the common practices: *k-fold cross-validation* — It tests the performance of the model on different unseen portions of the same type of data. The entire available data set is split intro k-folds of equal size. From this division, k-1 folds are used for the training and the *k*th fold for testing. Besides providing an indication of how the model would react to unseen data, it

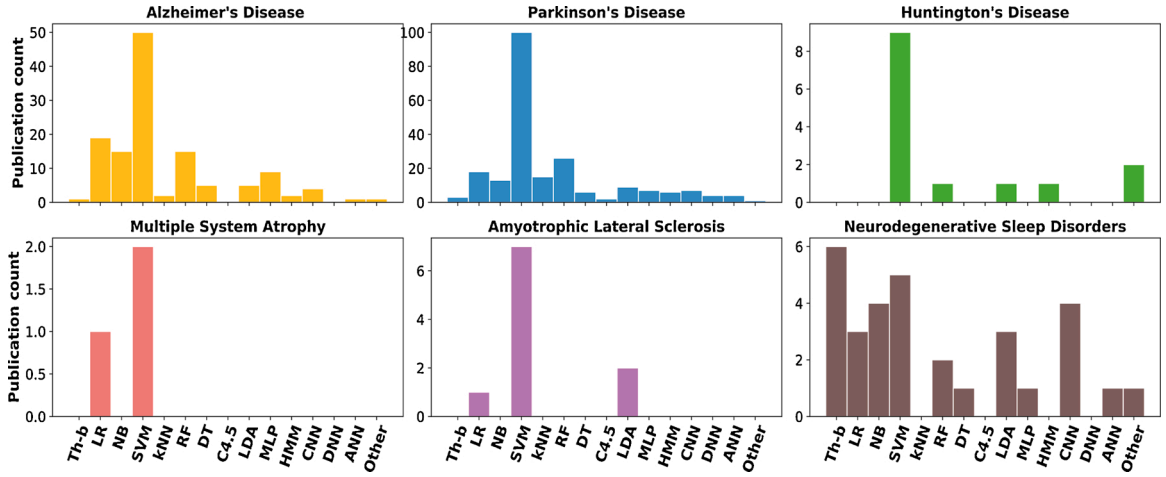

Fig. 4. Overview of the employed classification algorithms (as analyzed in this review) represented on a per disease basis. The most encountered algorithms include: Th-b — threshold based, LR — linear regression, NB — Naive Bayes, SVM — support vector machines, kNN — k-nearest neighbors, RF — random forests, DT — decision trees, LDA — linear discriminant analysis, MLP — multilayer perceptron, CNN — convolutional neural networks, ANN — artificial neural networks.

can also be useful when handling large amounts of data as the data is fed into the training and test phases in folds and not through large blocks; *leave-one out* — It is typically used with small datasets when using k-fold cross-validation would significantly reduce the amount of data available for training. In this case, the data from one subject is kept for testing, while the rest of the subjects are used for training. The testing and training sets are rotated until all subjects have been used for testing. Another variation of the leave-one-out validation is the leave-one-record out, where instead of using subjects, only one record (unit of the data set) is used for testing while the others are used in training. This technique is more resource consuming than k-fold cross-validation and is generally not recommended for large datasets; *hold out* — Part of the data set is kept for training while the other for testing. A typical division would be 80% training and 20% testing, but variations exist. By dividing the data set, this validation allows the evaluation of performance on completely unseen data. However, the single division into test and train sets can lead to a local optimum result, which would not generalize well to a real-world scenario.

9.4.2. Metrics

Among the exiting metrics employed in machine learning and information retrieval, some are more predominantly found when dealing with data from neurodegenerative diseases. We present here the most prevalent ones: *accuracy* — represents the ratio between the total number of correct predictions and the total number of predictions. It does not provide insights into the rate of true positive and true negative predictions while also ignoring per-class performance evaluation. An algorithm for differentiation between different diseases can have a high predictive power for one disease and an extremely low one for a different diseases. However, the overall accuracy would be at an acceptable level; *specificity* (true negative rate) — represents the number of true negatives from the total number of predictions that are correctly identified; *sensitivity* (recall or true positive rate) — represents the number of true positives over the total number of predictions. It gives an indication of how well the algorithm detects specific classes; *Area Under the Curve* (AUC) — it is a method suitable for evaluating multi-class problems. It estimates the area under the receiver operating characteristic curve (ROC) which relates the true positive to the true negative rates at different settings of the classifier; *F1-Score* — represents a harmonic mean between precision (positive predictive value) and recall (probability of detection); *Cohen's Kappa coefficient* — is a statistical method that is typically used to quantify inter-rater agreement. The Kappa coefficient is computed between test labels and the predicted values obtained as output from the classification; *Correlation coefficient* — provides a measure of the strength of similarity between the prediction result and the desired output.

10. Conclusions and future challenges

In this review, we provided an overview of the general trends in employing computational approaches for the monitoring and diagnosis of neurodegenerative diseases. We have focused our efforts on five neurodegenerative diseases representative for the entire spectrum of neurodegeneration: AD, PD, HD, MSA and ALS. Neurodegenerative diseases have been extensively studied in recent years with the help of computational approaches, especially via traditional machine learning or deep learning networks. Diseases that present a higher occurrence rate, such as Alzheimer's and Parkinson's disease, are more often investigated. The higher economic burden imposed by more prevalent diseases has pushed for faster results and led to more solutions for automatic diagnostic and health assessment systems. Many solutions propose methods that incorporate classification algorithms.

10.1. Current state of research

Datasets and evaluation. Many small, closed datasets tailored to specific diseases and symptoms are used in the existing research. Surprisingly, larger datasets are mostly public. However, the available annotated data is not yet capable of coping with the actual requirements of deep neural networks, to allow maximum performance. Another aspect is the large variation in proposed evaluation techniques and metrics, which makes results difficult to compare, even on the same data set. Usually, the same data set is used for training and testing with different data folds. Testing on different collections than the ones used for learning is not as common. There is no consensus on evaluation metrics. Confusion matrices are rarely used even when dealing with multi-class problems. Disease specific scales are used as a golden standard only for PD, e.g., UPDRS and H&Y, but similar scales are rarely used as a reference for the other neurodegenerative diseases.

Challenges in computational approaches. Most computational methods proposed for the study of neurodegenerative diseases make use of shallow networks and handcrafted features. Deep learning networks along with the extraction of features in an unsupervised manner might improve the performance of classification solutions. Since for some diseases and symptoms the data used for classification and study is scarce, generative adversial networks can be used to generate more datasets. Transfer learning techniques can also be considered when studying different diseases with similar symptomatology. For instance, if

a large data set for RBD or PLM recorded from PD patients is available, an algorithm can be developed and transfered to ALS or MSA sleep studies. The same could be applied for gait or speech abnormality detection.

10.2. Directions for development

Possible research directions. The authors have identified some areas that might be worth investigating: (i) *sleep in AD* — can show the effect of medication on the lifestyle of the patient; (ii) *differential diagnosis based on speech* — speech analysis for motor diseases such as PD, HD, MSA and ALS, lexical analysis for AD and other dementias. Using speech for differential diagnosis can be advantageous as microphones are available in many consumer devices; (iii) *use of EEG* — biomarkers can be developed for all neurodegenerative diseases. As EEG technology is non-invasive and less expensive than brain imaging, it can bring advantages and simplify the diagnostic process. Wearable EEG headsets can open even more possibilities in the diagnosis of neurodegenerative diseases; (iv) *memory testing applications* — differentiate between AD or other dementing diseases and MCI. Memory tests are currently delivered by medical professionals. By developing applications that focus on the ease of use, the diagnostic process can be simplified and made more accessible, while at the same time allowing for disease tracking; (v) *dual tasking* — early onset detection and tracking of dementing and mixed neurodegenerative disorders. By developing tasks that monitor both the cognitive ability and the motor functions of a patient, the progress of disease and risk for further injury can be determined. Dual tasks can be designed with the purpose of measuring the cognitive reserve of a patient. The concept of cognitive reserve is related to the ability of the brain to re-purpose its networks to counter the effects of neurodegeneration. In recent research, the presence of a higher cognitive reserve is indicative of a delayed disease onset or milder symptoms [198].

Applications. Few real-life available applications have been identified by the authors. Usability and adoption by the users was not detailed. Most of the identified applications were developed for PD. These make use of wearable inertial sensors or smartphones. The development is generally limited to one particular disease. As the classification of neurodegenerative diseases is discrete, based on clinical symptoms, the initial diagnosis is difficult as symptoms overlap. As the cause of the disease is not yet known and they cannot yet be treated, disease management focuses on managing the symptoms. An integrative approach looking at neurodegeneration as a continuum could take information from multiple sources (gait, voice, sleep, EEG, brain imaging, etc.). This would provide a global view on the disease. Thus allowing a better analysis of the symptoms and a subsequent better treatment management. It might also improve the initial diagnosis. The prediction of disease appearance and onset can also be improved by further developing techniques such as EEG biomarker extraction or sleep characterization. Although brain imaging is a powerful tool in disease diagnosis and monitoring, it is expensive, not easily accessible and might be difficult to use once the disease has advanced significantly. By providing more ubiquitous technologies for tracking, such as wearables, the progression and response to medication might be better observed.

Conflict of interest

The authors declare they have no conflict of interest.

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