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# Machine learning for Parkinson's disease and related disorders

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1 Book: Machine Learning for Brain Disorders

## 2 **Chapter 26**

# 3 **Machine learning for Parkinson’s disease and related** 4 **disorders**

5  
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15 **Running head (no more than 60 characters, including spaces):** Machine learning for  
16 Parkinson’s disease and related disorders.

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26

27 **Abstract** [*short abstract recommended (250 word at most); unstructured*]

28 Parkinson's disease is a complex heterogeneous neurodegenerative disorder characterized by  
29 the loss of dopamine neurons in the basal ganglia, resulting in many motor and non-motor  
30 symptoms. Although there is no cure to date, the dopamine replacement therapy can improve  
31 motor symptoms and the quality of life of the patients. The cardinal symptoms of this disorder  
32 are tremor, bradykinesia and rigidity, referred to as parkinsonism. Other related disorders, such  
33 as dementia with Lewy bodies, multiple system atrophy and progressive supranuclear palsy,  
34 share similar motor symptoms although they have different pathophysiology and are less  
35 responsive to the dopamine replacement therapy. Machine learning can be of great utility to  
36 better understand Parkinson's disease and related disorders and to improve patient care. Many  
37 challenges are still open, including early accurate diagnosis, differential diagnosis, better  
38 understanding of the pathologies, symptom detection and quantification, individual disease  
39 progression prediction, and personalized therapies. In this chapter, we review research works  
40 on Parkinson's disease and related disorders using machine learning.

41

42 **Keywords** [*5-10 keywords*]

43 Clinical decision support; deep learning; disease understanding; machine learning; multiple  
44 system atrophy; Parkinson's disease; parkinsonian syndromes; parkinsonism; precision  
45 medicine; progressive supranuclear palsy;

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## 49 **1. Introduction**

50 Parkinson's disease (PD) is the second most frequent neurodegenerative after Alzheimer's  
51 disease, affecting more than 6 million individuals worldwide, a prevalence which is expected  
52 to double with the next 10 years (1). It is characterized by the progressive degeneration of  
53 dopaminergic neurons in the *substantia nigra* associated with intracellular inclusions called  
54 Lewy bodies. These Lewy bodies are composed of protein aggregates enriched in  $\alpha$ -synuclein.  
55 Age is the greatest risk factor, but both environmental and genetic risk factors have been  
56 associated with PD. For instance, exposure to pesticides is a well-recognized risk factor for  
57 PD, whereas caffeine intake and smoking has been demonstrated to be protective (2). Although  
58 commonly sporadic, rare genetic forms of the disease have been described. More than 20 loci  
59 and associated genes have been identified to be responsible for autosomal dominant or  
60 recessive forms of the disease, and more than 90 genetic risk factors have been associated with  
61 sporadic PD (3). Although rare, genetic forms of the disease have brought important insights  
62 on the causes and pathological mechanisms of PD (4). Among them, aggregation and spreading  
63 of misfolded  $\alpha$ -synuclein, the protein enriched in Lewy bodies, is supposed to play a key role  
64 in the pathophysiology of the disease.

65         The loss of dopamine innervation of the basal ganglia network in the brain leads to the  
66 cardinal motor symptoms of the disease (parkinsonism): rest tremor, akinesia, and rigidity (2).  
67 However, the spreading of the synucleinopathy (aggregation of  $\alpha$ -synuclein protein) and  
68 neuronal loss outside the dopaminergic pathway is associated with other non-motor symptoms  
69 like anosmia, sleep disorders, dysautonomia, and progressive cognitive decline. Some of these  
70 symptoms, particularly anosmia, constipation and sleep disorders, can precede the motor phase  
71 during a long prodromal phase (5).

72         There is no cure for PD. The therapeutic strategy relies on the dopamine replacement  
73 therapy by levodopa or dopamine agonists, which alleviate motor symptoms. However, the

74 dopamine replacement therapy does not change the course of the disease, the progression being  
75 hampered by motor complications (motor fluctuations and abnormal movement called  
76 dyskinesia), related to both the progression of the neuronal loss and to pre- and post-synaptic  
77 plasticity induced by the treatment. In addition, the dopamine replacement therapy has no  
78 benefit on non-motor symptoms not related to the loss of dopaminergic neurons.

79 PD is the most frequent synucleinopathy. Other neurodegenerative diseases share some  
80 clinical and pathophysiological features of PD. Multiple system atrophy (MSA) is a rare  
81 disease associated with parkinsonism with low response to levodopa, early dysautonomia,  
82 and/or cerebellar symptoms (6). The synucleinopathy affects the substantia nigra, but also the  
83 striatum and the cerebellum, and Lewy bodies are also observed in glial cells. There are two  
84 variants of MSA: the parkinsonian variant (MSA-P) characterized by parkinsonism, and the  
85 cerebellar variant (MSA-C) characterized by gait ataxia with cerebellar dysarthria. Dementia  
86 with Lewy bodies (DLB), the second most common neurodegenerative dementia after  
87 Alzheimer's disease, is characterized by early cognitive decline, hallucinations, and levodopa-  
88 responsive motor symptoms (7). However, whether DLB and PD with dementia are really two  
89 distinct entities is still a matter of debate. There are also other rare atypical parkinsonism  
90 syndromes, not related to a synucleinopathy. Progressive supranuclear palsy (PSP) is a  
91 tauopathy (aggregation of tau protein) characterized by a non-responsive, axial predominant  
92 parkinsonism, early falls, supranuclear gaze palsy, and a frontal syndrome (8). The cortico-  
93 basal degeneration (CBD) is also a tauopathy with asymmetric parkinsonism with dystonia and  
94 cognitive dysfunction. Table 1 summarizes the characteristics of all these disorders.

95 Considering the complexity of these disorders, the lack of reliable biomarkers and the  
96 overlapping clinical presentation at the early stage, there is a need for more advanced  
97 approaches to support differential diagnosis. In addition, the pathophysiology of these  
98 disorders results from the complex interplay of multiple mechanisms. One current challenge is

99 to stratify patients according to specific mechanisms, and predict individual progression profile  
100 in order to move toward a more personalized medicine. Machine learning consists in extracting  
101 information from data by computer programs without providing explicit rules on what to  
102 extract, in the sense that machines learn by themselves which information to extract. Given the  
103 complexity of Parkinson's disease and its related disorders, there still exist many challenges  
104 and open questions for which machine learning could help increase knowledge on these  
105 disorders, in particular diagnosis, disease understanding and precision medicine, and create  
106 better clinical decision support systems. Table 2 summarizes the potential benefits of machine  
107 learning for Parkinson's disease and related disorders.

108         The rest of this chapter is organized as follows. We first present research works on the  
109 diagnosis of Parkinson's disease and the differential diagnosis between parkinsonian  
110 syndromes, including disease understanding (Section 2). We then focus on the detection and  
111 quantification of motor and non-motor symptoms in Parkinson's disease (Section 3). Disease  
112 progression in Parkinson's disease, with the prediction of individual progression trajectories,  
113 are presented in Section 4. We then describe research on the monitoring and adjustment of  
114 treatment in Parkinson's disease and discuss the limitations of machine learning in terms of  
115 causality (Section 5). Finally, we conclude on the existing literature discuss open questions and  
116 research works (Section 6). Table 3 summarizes the studies described in this chapter.

117

## 118 **2. Diagnosis**

119 Having an automated model being able to accurately diagnose one or several diseases has not  
120 only a concrete utility in clinical routine, but interpreting the decision process of the model  
121 may also help better understand these diseases. To assist diagnosis, two different classification  
122 tasks are usually considered: (i) being able to differentiate PD patients from healthy controls  
123 (HC), and (ii) being able to differentiate several parkinsonian syndromes from each other.

### 124 **2.1. Parkinson's disease diagnosis compared to healthy subjects**

125 Given the much larger prevalence of Parkinson's disease compared to the atypical parkinsonian  
126 syndromes, gathering data from PD patients and HC is naturally easier, especially easy-to-  
127 collect data from sensors compared to clinical, imaging or genetic data.

128 Digital technologies including wearable sensors, smartphone applications, and smart  
129 algorithms receive a strongly increasing interest and begin to move toward medical  
130 applications, particularly in PD (9). Two main types of sensor data are usually considered:  
131 voice data and motion data. Given that the cardinal symptoms of PD are motor, motion data is  
132 natural, but speech also involves motor muscles. Dysarthria, which is a motor speech disorder  
133 in which the muscles involved in producing speech are damaged, paralyzed, or weakened, is a  
134 symptom of PD.

#### 135 **2.1.1. PD diagnosis using motion data**

136 Several types of sensors have been investigated to collect motion data depending on the  
137 movements of interest.

138 Wahid and colleagues (10) investigated the discrimination between PD patients and  
139 healthy controls using gait data collected during self-selected walking. They extracted spatial-  
140 temporal features, such as stride length, stance time, swing time, and step length, from the  
141 signals, and investigated different strategies of data normalization using dimensionless

142 equations and multiple regression, and different machine learning algorithms such as naive  
143 Bayes (NB), k-nearest neighbors (kNN), support vector machines (SVM) and random forests  
144 (RF). They obtained the best predictive performance with the random forest trained on features  
145 normalized using multiple regression.

146 Mirelman and colleagues (*11*) also investigated gait and mobility measures that are  
147 indicative of PD and PD stages. They gathered data from sensors adhered to the participant's  
148 lower back, bilateral ankles and wrists, during short walks, and extracted gait features. They  
149 investigated several strategies to perform feature selection, and use a random under-sampling  
150 boosting classification algorithm to tackle class imbalance. When comparing PD patients with  
151 mild PD severity (Hoehn & Yahr stage 1) to healthy controls, they obtained good  
152 discriminative performance (84% sensitivity, 80% specificity). Most discriminative features  
153 were extracted from the upper-limb sensors, with the remaining features extracted from the  
154 trunk sensor, while the lower-limb sensors did not contribute to discrimination accuracy.

155 Kostikis and colleagues (*12*) investigated upper limb tremor using a smartphone-  
156 based tool. Signals from the phone's accelerometer and gyroscope were computed, from which  
157 features were extracted. They trained several machine learning algorithms, including random  
158 forest, naive Bayes, logistic regression (LR) and support vector machine, using these features  
159 as input, and obtained the highest discriminative performance between PD patients and HC  
160 with the random forest model.

161 Kotsavasiloglou and colleagues (*13*) investigated the use of a pen-and-tablet device  
162 to study the differences in hand movement and muscle coordination between PD patients and  
163 HC. Data consisted of the trajectory of the pen's tip and on the pad's surface from drawings of  
164 simple horizontal lines, from which they extracted features. They investigated several machine  
165 learning algorithms such as logistic regression, support vector machine and random forest, and



166 used nested cross-validation to perform feature selection. They obtained the highest  
167 discriminative performance with the naive Bayes model.

### 168 **2.1.2. PD diagnosis using voice data**

169 Voice data is usually recorded from high-quality microphones or from smartphones during  
170 specific vocal tasks focused on characteristics such as phonation and speech. Features are then  
171 extracted from the corresponding signals and used as input to machine learning classification  
172 algorithms.

173 Amato and colleagues (*14*) analyzed specific phonetic groups in native Italian  
174 speakers, extracted several spectral moments from the signals and trained a SVM algorithm on  
175 these extracted features to distinguish PD patients from HC. They first worked on a public  
176 dataset called Italian Parkinson's Voice and Speech<sup>1</sup>, with data recorded in ideal publications,  
177 and obtained great performance on the validation and test sets. They then merged this public  
178 data set with a data set that they collected, with data being recorded in more realistic,  
179 suboptimal conditions, and obtained good but lower performance on the validation and test sets  
180 of this merged data set. Experiments with training on one single data set and validation on the  
181 other data set were not performed, but it would have been interesting to estimate how well a  
182 trained model could generalize on other data sets with data being recorded in different  
183 conditions.

184 Jeancolas and colleagues (*15*) investigated the early diagnosis of PD and possible  
185 gender differences in voice data. They used a pre-trained deep neural network focused on  
186 speaker recognition system to extract features and obtained a higher performance than with a  
187 standard multidimensional Gaussian mixture model, although the increase was more important

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<sup>1</sup> <https://iee-dataport.org/open-access/italian-parkinsons-voice-and-speech>

188 among men than women. They also investigated the impact of the quality of the recordings  
189 (using either a high-quality microphone or a telephone) and obtained the same conclusions in  
190 both cases.

191 In another study, Jeancolas and colleagues (**16**) investigated the differentiation  
192 between early PD patients and patients with idiopathic rapid eye movement sleep behavior  
193 disorders (iRBD), which are important risk factors to develop PD in the near future. They  
194 extracted features related to prosody, phonation, speech fluency and rhythm abilities from  
195 speech recordings. They once again obtained a higher predictive performance among men than  
196 women in the PD vs HC classification task, and a better discriminative power for this  
197 classification task than for the iRBD vs HC one, suggesting that discriminating iRBD patients  
198 from HC using voice data is a much harder task, but it is also probably a most useful one in  
199 practice.

200 Quan and colleagues (**17**) investigated the extraction of global static features (from  
201 the whole signals) and local dynamic features (using a sliding window on the signals) from  
202 voice data during articulation tasks. They trained standard machine learning classification  
203 algorithms, such as decision trees (DT), k-nearest neighbors, naive Bayes and support vector  
204 machines, using the static features, while they trained a recurrent neural network, more  
205 specifically a bidirectional long short-term memory (LSTM), on the dynamic features, and  
206 obtained a higher predictive performance with the deep learning approach.

207 Although many studies reported high predictive performances, some results must be  
208 taken with caution. Indeed, a recent study reported methodological issues in several studies,  
209 including record-wise cross-validation instead of subject-wise cross-validation, high imbalance  
210 in ages between PD patients and HC, and performance metrics computed on the validation  
211 folds of k-fold cross-validation and not on an independent test set, which may lead to overly  
212 optimistic results (**18**).

### 2.1.3. PD diagnosis using imaging data

The diagnosis of PD remains based on its clinical presentation (19). Imaging of dopaminergic terminals loss can be assessed using nuclear imaging, but it is not recommended in clinical routine, and does not differentiate PD from other related disorders associated with dopamine neuron loss (20). Standard brain magnetic resonance imaging (MRI) is normal in PD. However, several new markers have been recently been investigated in several studies, with mixed results.

Adeli and colleagues (21) investigated the use of T1-weighted anatomical MRI data to differentiate PD patients from HC. They developed a joint feature-sample selection algorithm in order to select an optimal subset of both features and samples from a training set, and a robust classification framework that performs denoising of the selected features and samples then learns a classification model. They analyzed data from 374 PD patients and 169 HC from the Parkinson's Progression Markers Initiative<sup>2</sup> (PPMI) cohort, and included white matter, gray matter and cerebrospinal fluid measurements from 98 regions of interest. The combination of the proposed feature selection/extraction method and classifier achieved the highest predictive accuracy (0.819), being significantly better than almost every other combination of a feature selection/extraction method and a classification algorithm.

Solana-Lavalle and Rosas-Romero (22) investigated the use of voxel-based morphometry features extracted from T1-weighted anatomical MRI to perform a PD vs HC classification task. Their pipeline consisted of 5 stages: (i) identification of regions of interest using voxel-based morphometry, (ii) analysis of these regions for PD detection, (iii) feature extraction based on first- and second-order statistics, (iv) feature selection based on principal

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<sup>2</sup> <https://www.ppmi-info.org>

235 component analysis, and (v) classification with 10-fold cross-validation based on 7 different  
236 algorithms (including k-nearest neighbors, support vector machine, random forest, naive Bayes  
237 and logistic regression). They obtained excellent predictive performance for both male and  
238 female genders and for both 1.5T and 3T MRI scans (accuracy scores ranging from 0.93 to  
239 0.99 for the best classification algorithms). However, cross-validation was performed very late  
240 in their pipeline (after the feature subset selection), which could lead to biased models and  
241 overly optimistic predictive performances.

242         Mudali and colleagues (23) investigated another modality, [18F]-fluorodeoxyglucose  
243 positron emission tomography (FDG-PET), to compare 20 PD patients and 18 HC. They  
244 applied the subprofile model/principal component analysis method to extract features from the  
245 images. They considered a DT algorithm and used leave-one-out cross-validation to evaluate  
246 the predictive performance of the models. They obtained really low predictive performance  
247 (50% sensitivity, 45% specificity), close to chance level.

248         Overall, it is unclear if machine learning applied to anatomical MRI or FDG-PET can  
249 bring added value for the diagnosis of PD. However, advanced MRI sequences have the  
250 potential to bring much more valuable information (24).

## 251 **2.2. Differential diagnosis**

252 The PD vs HC binary classification task has limited utility as, even at the early stage of PD,  
253 patients have clinical symptoms strongly suggesting that they suffer from a movement disorder,  
254 and thus are not healthy subjects. However, the accurate early diagnosis of parkinsonian  
255 syndromes is difficult but needed due to the different pathologies and thus the different care.  
256 Although one study investigated the differential diagnosis using sensor-based gait analysis  
257 (25), most studies investigated it using imaging data, particularly diffusion MRI.

258         Huppertz and colleagues (26) investigated the differential diagnosis with data from a  
259 relatively large cohort (73 HC, 204 PD, 106 PSP, 20 MSA-C and 60 MSA-P). Using atlas-

260 based volumetry of brain MRI data, they extracted volumes in several regions of interest, and  
261 trained and evaluated a linear SVM algorithm using leave-one-out cross-validation. They  
262 obtained good predictive performance in most binary classification tasks, and showed that  
263 midbrain, basal ganglia, and cerebellar peduncles were the most relevant regions.

264         A landmark study on this topic was published in 2019 by Archer and colleagues (27),  
265 with diffusion-weighted MRI data being collected for 1002 subjects from 17 MRI centers in  
266 Austria, Germany and the USA. They extracted 60 free-water and 60 free-water-corrected  
267 fractional anisotropy values from diffusion-weighted MRI data, and the other features  
268 consisted of the third part of the Movement Disorder Society-Sponsored revision of the Unified  
269 Parkinson's Disease Rating Scale (MDS-UPDRS III), sex and age. They trained several SVM  
270 models and showed that the model trained using MDS-UPDRS III (with sex and age also, for  
271 all the models) performed poorly in most classification tasks, whereas the model trained using  
272 DWI features had much higher predictive performance (particularly for the MSA vs PSP task)  
273 and adding MDS-UPDRS III to this model did not improve the performance.

274         More recently, Chougar and colleagues (28) investigated the replication of such  
275 differential diagnosis models in clinical practice on different MRI systems. Using MRI data  
276 from 119 PD, 51 PSP, 35 MSA-P, 23 MSA-C and 94 HC, split into a training cohort (n=179)  
277 and a replication cohort (n=143), they extracted volumes and diffusion tensor imaging (DTI)  
278 features (fractional anisotropy, mean diffusivity, axial diffusivity and radial diffusivity) in 13  
279 regions of interest. They investigated two feature normalization strategies (one based on the  
280 data of all subjects in the training set, and one based on the data of HC for each MRI system to  
281 tackle the different feature distributions, in particular for DTI features, because of the use of  
282 different MRI systems) and four standard machine learning algorithms, including logistic  
283 regression, support vector machines, random forest. They obtained high performances in the  
284 replication cohort for many binary classification tasks (PD vs PSP, PD vs MSA-C, PSP vs

285 MSA-C, PD vs atypical parkinsonism), but lower performances for other classification tasks  
286 involving MSA-P patients (PD vs MSA-P, MSA-C vs MSA-P). They showed that adding DTI  
287 features did not improve performance compared to using volumes only, and that the usual  
288 normalization strategy worked best in this case.

289 Shinde and colleagues (29) investigated the automatic extraction of contrast ratios of  
290 the substantia nigra pars compacta from neuromelanin sensitive MRI using a convolutional  
291 neural network. Based on the class activation maps, they identified that the left side of  
292 substantia nigra pars compacta played a more important role in the decision of the model  
293 compared to the right side, in agreement with the concept of asymmetry in PD.

294 A recent study (30) investigated the use of positron emission tomography of the  
295 translocator protein, expressed by glial cells, and extracted normalized standardized uptake  
296 value images and normalized total distribution volume images. Using a linear discriminant  
297 analysis algorithm with leave-one-subject-out cross-validation, they obtained great  
298 discriminative power between MSA and PD patients, with better performance with normalized  
299 total distribution volume images.

### 300 **2.3. Disease understanding**

301 Rather than focusing on the diagnosis of Parkinson's disease itself, several studies were more  
302 focused on interpreting the trained machine learning models in order to better understand the  
303 mechanisms of Parkinson's disease.

304 Khawaldeh and colleagues (31) investigated the task-related modulation of local field  
305 potentials of the subthalamic nucleus before and during voluntary upper and lower limb  
306 movements in 18 consecutive Parkinson's disease patients undergoing deep brain stimulation  
307 (DBS) surgery of the subthalamic nucleus in order to improve motor symptoms. Using a naive  
308 Bayes classification algorithm, they obtained chance-level performance at rest, but much  
309 higher performance during the pre-cue, pre-movement onset and post-movement onset tasks.

310 They showed that the presence of bursts of local field potential activity in the alpha, and even  
311 more so, in the beta frequency band significantly compromised the prediction of the limb to be  
312 moved, concluding that low frequency bursts restrict the capacity of the basal ganglia system  
313 to encode physiologically relevant information about intended actions.

314 Poston and colleagues (32) investigated brain mechanisms that allow some PD patients  
315 with severe dopamine neuron loss to remain cognitively normal. Using functional MRI data  
316 from PD patients without cognitive impairment and from HC collected during a working  
317 memory task, they trained a support vector machine classifier and identified robust differences  
318 in putamen activation patterns, providing novel evidence that PD patients maintain normal  
319 cognitive performance through compensatory hyperactivation of the putamen.

320 Trezzi and colleagues (33) investigated cerebrospinal fluid biomarkers, and more  
321 precisely the metabolome, in early-stage PD. The logistic regression model trained on such  
322 data provided good discriminative power, and the most associated biomarkers were mannose,  
323 threonic acid and fructose. These biomarkers were associated with antioxidative stress  
324 response, glycation, and inflammation, and may help better understand PD pathogenesis.

325 Vanneste and colleagues (34) investigated thalamocortical dysrhythmia, which is a  
326 model proposed to explain divergent neurological disorders, and is characterized by a common  
327 oscillatory pattern in which resting-state alpha activity is replaced by cross-frequency coupling  
328 of low- and high-frequency oscillations. The trained support vector machine model identified  
329 specific brain regions that provided good discriminative power between PD patients and HC,  
330 including subgenual anterior cingulate cortex, posterior cingulate cortex, parahippocampus,  
331 dorsal anterior cingulate cortex, motor cortex. Another model also identified brain areas that  
332 are common to the pathology of Parkinson's disease, pain, tinnitus, and depression, including  
333 dorsal anterior cingulate cortex and parahippocampal area.

### 334 **3. Symptom detection and quantification**

335 Given the complexity and heterogeneity of Parkinson's disease, prompt accurate assessment of  
336 symptoms is needed. A detailed scale, called the Movement Disorders Society-Sponsored  
337 revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (35), is currently the  
338 gold standard to assess motor (and non-motor) features of PD patients by movement disorders  
339 specialists. The scale is divided into four sections. The first two sections allow for assessing  
340 the non-motor and motor activities of daily living respectively, while the third section consists  
341 of a motor exam and the fourth section allows for assessing motor complications.

342         Nonetheless, the MDS-UPDRS has several limitations. First, it requires time (30-45  
343 minutes for the full scale) and a trained movement disorder specialist to fill it, limiting its use  
344 during clinical routine visits. Second, part of subjectivity from a human evaluation, and thus  
345 variance in the MDS-UPDRS scores, cannot be excluded, with a recent study suggesting that  
346 MDS-UPDRS scores contain a substantial amount of variance (36). Moreover, other scales are  
347 typically used to more precisely assess non-motor symptoms such as depression, anxiety and  
348 cognition. Finally, scales are addressed during a visit at the hospital and may not reflect the  
349 symptoms in a more ecological setting, at home, during the daily life of the patient. Automatic  
350 detection and quantification of symptoms using machine learning may help tackle these  
351 limitations, and several studies investigated this topic. In the remaining of this section, we  
352 group these studies based on the symptoms investigated.

#### 353 **3.1. Freezing of gait**

354 Freezing of gait (FOG) is a common motor symptom and is associated with life-threatening  
355 accidents such as falls. Prompt identification or prediction of freezing of gait episodes is thus  
356 needed.

357         Ahlrichs and colleagues (37) investigated freezing of gait in 20 PD patients (8 with  
358 FOG, 12 without FOG), split into a training set (15 patients) and a test set (5 patients). They



359 collected sensor (accelerometer, gyroscope and magnetometer) data during scripted activities  
360 (e.g., walking around the apartment, carrying a full glass of water from the kitchen to another  
361 room) and non-scripted activities (e.g., answering the phone). Two recording sessions were  
362 considered: one in “OFF” motor state and one in “ON” motor state and the data was labeled by  
363 experienced clinicians based on the corresponding video recordings. The task was a binary  
364 classification tasks (FOG vs no FOG) for each window. They extracted sub-signals from the  
365 whole signals using a sliding window, then extracted features and in the time and frequency  
366 domains for each sub-signal. They trained two SVM algorithms (one with a linear kernel, one  
367 with a Gaussian kernel) and obtained high and better results with the linear kernel.

368 Aich and colleagues (38) gathered sensor data for 36 PD patients with FOG and 15 PD  
369 patients without FOG from two wearable triaxial accelerometers during clinical experiments.  
370 They extracted features, such step time, stride time, step length, stride length and walking  
371 speed, from the signals. They trained several classic machine learning classification algorithms  
372 (SVM, kNN, DT, NB) and obtained good predictive performances with all of them, although  
373 the SVM model had the highest mean accuracy on the test sets of the cross-validation  
374 procedure.

375 Borzi and colleagues (39) collected data from two inertial sensors placed on each shin  
376 of the 11 PD patients during the “timed up and go” test in order to investigate FOG and pre-  
377 FOG detection. They extracted features in the time and frequency domains and trained decision  
378 tree algorithms. They obtained great predictive performance to detect FOG episodes, but lower  
379 performance to predict pre-FOG episodes, with the performance decreasing even more as the  
380 window length increased.

381 Dvorani and colleagues (40) were interested in detecting foot motion phases using a  
382 shoe-placed inertial sensor in order to detect FOG episodes. They extracted ten features,  
383 including stride length, maximum gait velocity and step duration, from each motion phase, and

384 trained a SVM algorithm to detect FOG episodes. They obtained great performance when using  
385 features from the current and two preceding motion phases, but lower performance when using  
386 only features from the two preceding motion phases, highlighting the higher difficulty to  
387 predict FOG episodes in advance. Shalin and colleagues (41) reached the same conclusion  
388 using plantar-pressure data and a long short-term memory neural network.

### 389 **3.2. Bradykinesia and tremor**

390 Bradykinesia and tremor are two other motor-symptoms that are frequently investigated for  
391 automatic assessment.

392 Park and colleagues (42) investigated automated rating for resting tremor and  
393 bradykinesia from video clips of resting tremor and finger tapping of the bilateral upper limbs.  
394 They extracted several features from the video clips, including resting tremor amplitude and  
395 finger tapping speed, amplitude and fatigue, using a pre-trained deep learning model. These  
396 features were used as input of a SVM algorithm to predict the corresponding scores from the  
397 MDS-UPDRS scale. For resting tremors, the automated approach had excellent reliability  
398 range with the gold standard rating and higher performance than that of non-trained human  
399 rater. For finger tapping, the automated approach had good reliability range with the gold  
400 standard rating and similar performance than that of non-trained human rater.

401 Kim and colleagues (43) performed a study in which they investigated tremor severity  
402 using 3-dimensional acceleration and gyroscope data obtained from wearable device. They  
403 investigated a convolutional neural network to automatically extract features and perform  
404 classification, compared to extracting defined features from the time and frequency domains  
405 and training standard machine learning algorithms (random forest, naive Bayes, linear  
406 regression, support vector machines) using these features. They obtained better higher  
407 predictive performance with the deep learning approach than the standard machine learning

408 approach. Eskofier and colleagues (44) obtained similar results using inertial measurement  
409 units collected during motor tasks.

### 410 **3.3. Cognition**

411 Cognitive impairment is frequent in PD, with the point prevalence of PD dementia being  
412 around 30% and the cumulative prevalence for patients surviving more than 10 years being at  
413 least 75% (45). Due to its high negative impact on the quality of life of PD patients and their  
414 caregivers, it is important to identify and quantify cognitive impairment. Several scales to  
415 assess cognition already exist, such as the Mini-Mental State Examination and the Montreal  
416 Cognitive Assessment, but automatic assessment of cognition could be helpful.

417 Abós and colleagues (46) investigated discriminating cognitive status in PD through  
418 functional connectomics. Using resting-state functional MRI data, they extracted features  
419 consisting of connection-wise pattern of functional connectivity. They performed feature  
420 selection using randomized logistic regression with leave-one-out cross-validation, then trained  
421 a SVM algorithm. They obtained good discriminative performance between PD patients with  
422 mild cognitive impairment and with no cognitive impairment, but could not report significant  
423 connectivity reductions between both groups.

424 Betrouni and colleagues (47) investigated the use of electroencephalograms to  
425 automatically assess their cognitive status. A cluster analysis of the neuropsychological  
426 assessments of 118 PD patients revealed 5 cognition clusters. They extracted quantitative  
427 features from the electroencephalograms and performed feature selection based on Pearson  
428 correlation tests. They trained two machine learning algorithms (kNN and SVM), using a 5-  
429 fold cross-validation procedure that was repeated 5 times, and obtained good similar predictive  
430 performances for the 5-class classification task with both models.

431 García and colleagues (48) investigated cognitive decline using dysarthric symptoms.  
432 They extracted prosodic, articulatory and phonemic identifiability features from speech signals

433 recorded during the reading of two narratives. Using a SVM algorithm and nested cross-  
434 validation, they obtained correct discriminative performance (area under the receiver operating  
435 characteristics curve of 0.76), with the highest performance being obtained using phonemic  
436 identifiability features.

437 Morales and colleagues (49) investigated the classification of PD patients with no  
438 cognitive impairment (n=16), with mild cognitive impairment (n=15) and with dementia  
439 (n=14). They trained several variants of the naive Bayes algorithm and one SVM algorithm on  
440 112 MRI features consisting of volumes of subcortical structures and thickness of cortical  
441 parcels, and obtained good discriminative performance in the 3 binary classification tasks, the  
442 lower performance corresponding to the differentiation between PD patients with no cognitive  
443 impairment with mild cognitive impairment. The most important features involved the  
444 following brain regions: left cerebral cortex, left caudate, left entorhinal, right inferior left  
445 hippocampus, and brain stem.

446 A recent study (50) also investigated MRI data, more specifically quantitative  
447 susceptibility mapping images parcellated into 20 regions of interest, for early detection of  
448 cognitive impairment in PD. Using tree-based ensemble machine learning algorithms, such as  
449 random forest and extreme gradient boosting, they obtained acceptable predictive performance  
450 and showed that the features corresponding to the caudate nucleus were important for  
451 classification and also inversely correlated with Montreal Cognitive Assessment scores.

### 452 **3.4. Other symptoms**

453 Although less prevalent in the literature, studies also investigated other PD symptoms such as  
454 falls and motor severity.

455 An early study by Hannink and colleagues (51) was performed to investigate gait  
456 parameter extraction from sensor data using convolutional neural networks. Using 3d-  
457 accelerometer and 3d-gyroscope data from 99 geriatric patients, the objective was to predict

458 the stride length and width, the foot angle, and the heel and toe contact times. They investigated  
459 two approaches to tackle this multi-output regression task, training either a single convolutional  
460 neural network to predict the five outcomes, or training a convolutional neural network for  
461 each outcome, and obtained better performance on an independent test set with the latter  
462 approach. Although the considered population was not parkinsonian, the prevalence of gait  
463 symptoms in this population and the obtained results might be relevant to better understand  
464 gait in this population. Lu and colleagues (52) investigated gait in PD, as measured by MDS-  
465 UPDRS item 3.10, which does not include freezing of gait. They collected video recordings of  
466 MDS-UPDRS exams from 55 participants which were scored by three different trained  
467 movement disorder neurologists, and the ground truth score was defined using majority voting  
468 among the three raters. They performed skeleton extraction from the videos and trained a  
469 convolutional neural network, with regularization using rater confusion estimation to tackle  
470 noise in labels, to predict gait severity. They obtained correct performance on the test set (72%  
471 accuracy with majority voting, 84% accuracy with the model predicting at least one of the  
472 raters' scores).

473 Gao and colleagues (53) investigated falls in two data sets independently collected at  
474 two different sites. Using clinical scores as input, they trained several classic machine learning  
475 classification algorithms to differentiate fallers from non-fallers. They obtained acceptable  
476 predictive performance in both data sets when training and evaluating (using cross-validation)  
477 a model in each data set independently. They also showed that the predictive performance was  
478 lower when training the model on one data set and evaluating it on the other data set, which is  
479 not surprising, but it is important to have this possible issue in mind when a model is not  
480 evaluated on a different cohort.

## 481 **4. Disease progression**

482 Given the complexity and heterogeneity of Parkinson's, prediction of disease progression with  
483 individual trajectories is challenging. Two subtypes of PD, one with more postural instability  
484 and gait difficulty and the other one with more tremor symptoms, are already known.  
485 Nonetheless, there are other motor symptoms in PD and many PD symptoms are non-motor,  
486 thus deeper knowledge is required to understand disease progression.

### 487 **4.1. Disease subtypes**

488 Several studies focused on the identification of more specific disease subtypes than the two  
489 aforementioned well-known ones characterized by postural instability and gait difficulty for  
490 one, and tremor-predominant for the other.

491         Severson and colleagues (54) worked on the development of a statistical progression  
492 model of Parkinson's disease accounting for intra-individual and inter-individual variability,  
493 as well as medication effects. They built a contrastive latent variable model followed by a  
494 personalized input-output hidden Markov model to define disease states and assessed the  
495 clinical significance of the states on seven key motor or cognitive outcomes (mild cognitive  
496 impairment, dementia, dyskinesia, presence of motor fluctuations, functional impairment from  
497 motor fluctuations, Hoehn & Yahr score, and death). They identified eight disease states that  
498 were primarily differentiated by functional impairment, tremor, bradykinesia, and  
499 neuropsychiatric measures. The terminal state had the highest prevalence of key clinical  
500 outcomes, including almost every recorded instance of dementia. The discovered states were  
501 non-sequential, with overlapping disease progression trajectories, supporting the use of non-  
502 deterministic disease progression models, and suggesting that static subtype assignment might  
503 be ineffective at capturing the full spectrum of PD progression.

504         Salmanpour and colleagues (55) performed a longitudinal clustering analysis and  
505 prediction PD progression. They extracted almost a thousand features, including motor, non-

506 motor, and radiomics features. They performed a cross-sectional clustering analysis and  
507 identified 3 distinct progression trajectories, with two trajectories being characterized by  
508 disease escalation and the other trajectory by disease stability. They also investigated the  
509 prediction of progression trajectories from early stage (baseline and year 1) data and obtained  
510 the highest predictive performance with a probabilistic neural network.

## 511 **4.2. Prediction of future motor and non-motor symptoms**

512 Prediction of future symptoms and individual disease trajectories was the main focus of several  
513 studies.

514 Oxtoby and colleagues (56) aimed at estimating the sequence of clinical and  
515 neurodegeneration events, and variability in this sequence, using data-driven disease  
516 progression modelling, with a focus on PD patients with higher risk of developing dementia  
517 (defined as PD patients being diagnosed at age 65 or later). They analyzed baseline visit data  
518 from two separate cohorts: a local discovery cohort (100 PD patients and 33 HC) and a  
519 replication cohort (PPMI study, 350 PD patients and 127 HC). They considered 42 features,  
520 including 8 clinical/cognitive measures, 6 vision measures, 4 retinal measures, 8 regional  
521 measures of cortical thickness, 4 measures of white matter neurodegeneration in the substantia  
522 nigra, and 12 regional measures of brain iron content. They trained event-based models that  
523 incorporate non-parametric mixture modelling using 10 5-fold cross-validation procedures to  
524 estimate the robustness of the models. The authors showed that Parkinson's progression in  
525 patients at higher risk of developing dementia starts with classic prodromal features of PD  
526 (sleep and olfactory disorders), followed by early deficits in visual abilities and increased brain  
527 iron content, followed later by a less certain ordering of neurodegeneration in the substantia  
528 nigra and cortex, neuropsychological cognitive deficits, retinal thinning in dopamine layers,  
529 and further visual deficits. Their results support the growing piece of evidence that visual  
530 processing specifically is affected early in PD patients with high risk of developing dementia.

531           Latourelle and colleagues (57) investigated the development of predictive models of  
532 motor progression using longitudinal clinical, molecular and genetic data. More specifically,  
533 the objective was to predict the annual rate of changes in combined scores from the second and  
534 third parts of the MDS-UPDRS. The trained model showed strong performance in the training  
535 cohort (using 5-fold cross-validation), and lower but still significant performance in an  
536 independent replication cohort. The most relevant features included baseline MDS-UPDRS  
537 motor score, sex, and age, as well as a novel PD specific epistatic interaction. Genetic variation  
538 was the most useful prediction of motor progression, and baseline CSF biomarkers had a lower  
539 but still significant effect on predicting motor progression. They also performed simulations  
540 with the trained model and concluded that incorporating the predicted rates of motor  
541 progression into the final models of treatment effect reduced the variability in the study  
542 outcome, allowing significant differences to be detected at sample sizes up to 20% smaller than  
543 in naive trials.

544           Ahmadi Tastegar and colleagues (58) investigated the prediction of longitudinal  
545 clinical outcomes after 2-year follow-up from baseline and 1-year follow-up data. They also  
546 measured 27 inflammatory cytokines and chemokines in serum at baseline and after 1 year to  
547 investigate cytokine stability. Training random forest algorithms, the best prediction models  
548 were for motor symptom severity scales (Hoehn & Yahr stage and MDS-UPDRS III total  
549 score), and several inflammatory cytokine and chemokine features were among the most  
550 relevant features to predict Hoehn and Yahr stage and MDS-UPDRS III total score, giving  
551 evidence that peripheral cytokines may have utility for aiding prediction of PD progression  
552 using machine learning models.

553           Amara and colleagues (59) investigated the prediction of future incidents of excessive  
554 daytime sleepiness. They trained a random survival forest using 33 baseline variables,  
555 including anxiety, depression, rapid eye movement sleep, cognitive scores,  $\alpha$ -synuclein, p-tau,



556 t-tau and ApoE  $\epsilon$ 4 status. The performance of the model was only marginally better than  
557 random guess, but the strongest predictive features were p-tau and t-tau.

558 Couronné and colleagues (**60**) performed longitudinal data analysis to predict patient-  
559 specific trajectories. They proposed to use a generative mixed effect model that considers the  
560 progression trajectories as curves on a Riemannian manifold and that can handle missing  
561 values. They applied their model to PD progression with joint modelling of two features (MDS-  
562 UPDRS III total score and striatal binding ration in right caudate). Interpretation of the model  
563 revealed that patients with later onset progress significantly faster and that  $\alpha$ -synuclein mean  
564 level was correlated with PD onset.

565 Faouzi and colleagues (**61**) investigated the prediction of future impulse control  
566 disorders (psychiatric disorders characterized by the inability to resist an urge or an impulse  
567 and which include a wide range of types including compulsive shopping, internet addiction,  
568 and hypersexuality for instance) in Parkinson's disease. The objective of their study was to  
569 predict the presence or absence of these disorders at the next clinical visit of a given patient.  
570 Using clinical and genetic data, they trained several machine learning models on a training  
571 cohort and evaluated the models on the training cohort (using cross-validation) and on an  
572 independent replication cohort. They showed that a recurrent neural network model achieved  
573 significantly better performance than a trivial model (predicting the status at the next visit with  
574 the status at the most recent visit), but the increase in performance was too small to be deemed  
575 clinically relevant. Nevertheless, this proof-of-concept study highlights the potential of  
576 machine learning for such prediction.

## 577 **5. Treatment adjustment and adverse event prevention**

578 Being able to predict future adverse events in Parkinson's disease is useful, but being able to  
579 prevent them would be even more useful. Parkinson's disease is one of the few  
580 neurodegenerative diseases where current therapies can greatly improve the quality of life the  
581 patients, but these therapies also have adverse effects. Providing personalized adapted therapies  
582 to every patient is of high importance.

583 Machine learning allows for unveiling complex correlations or patterns from data.  
584 However, correlation does not imply causality: if two variables are correlated, one variable  
585 does not necessarily cause an effect on the other. Therefore, standard machine learning is not  
586 always well adapted to draw conclusions for personalized therapies. Ultimately, clinical trials  
587 with a specific hypothesis tested are the best solution to draw causality effect conclusions.  
588 Nonetheless, several machine learning approaches can investigate causality effects. Causal  
589 inference, that is being able to discover which variables have which impacts on which other  
590 variables, is an open research topic in machine learning, but usually requires a lot of data,  
591 limiting its use in Parkinson's disease. Nonetheless, exploratory studies suggesting potential  
592 options for personalized therapies and adverse event prevention have been published.

### 593 **5.1. Dopamine replacement therapy**

594 Dopamine replacement therapy, as a way to compensate the loss of dopamine neurons in the  
595 brain, is the most common therapy due to its efficacy and simplicity (drug intake). Nonetheless,  
596 it also comes with adverse effects and long-term motor complications such as motor  
597 fluctuations (worsening or reappearance of motor symptoms before the next drug intake) and  
598 dyskinesia (involuntary muscle movements) (62).

599 Yang and colleagues (63) investigated utility of amplitude of low-frequency fluctuation  
600 computed from functional MRI data of 38 PD patients in order to predict individual patient's  
601 response to levodopa treatment. They applied principal component analysis to perform

602 dimensionality reduction and trained gradient tree boosting algorithms to discriminate between  
603 moderate and superior responders to levodopa treatment. Treatment efficacy was defined based  
604 on motor symptoms improvement from the state of medication off to medication on, as assessed  
605 by MDS-UPDRS III total score. They obtained great discriminative performance between both  
606 groups, even though no significant difference in clinical data was observed between both  
607 groups. The mainly contributed regions for both models included the bilateral primary motor  
608 cortex, the occipital cortex, the cerebellum, and the basal ganglia. These results suggest the  
609 potential utility of amplitude of low-frequency fluctuation as promising predictive markers of  
610 dopaminergic therapy response in PD patients.

611         Kim and colleagues (64) investigated the use of reinforcement learning to predict  
612 optimal treatment for reducing motor symptoms. They derived clinically relevant disease states  
613 and an optimal combination of medications for each of them by using policy iteration of the  
614 Markov decision process. Their model achieved a lower level of motor symptom severity  
615 scores than what clinicians did, whereas the clinicians' medication rules were more consistent  
616 than their model. Their model followed the clinician's medication rules in most cases but also  
617 suggested some changes, which leads to the difference in lowering symptoms severity. This  
618 proof of concept showed the potential utility of reinforcement learning to derive optimal  
619 treatment strategies.

## 620 **5.2. Deep brain stimulation**

621 Deep brain stimulation is a neurosurgical procedure that uses implanted electrodes and  
622 electrical stimulation, and has proven efficacy in advanced Parkinson's disease by decreasing  
623 motor fluctuations, dyskinesia, and improving quality of life (65). The most commonly  
624 stimulated region is the subthalamic nucleus, but the globus pallidus is sometimes preferred.  
625 Although DBS usually greatly improves the motor symptoms, it also has downsides, such as

626 requiring personalized parameters and potential adverse events such as postoperative cognitive  
627 decline.

628         Boutet and colleagues (66) investigated the prediction of optimal deep brain stimulation  
629 parameters from functional MRI data. They extracted blood-oxygen-level-dependent (BOLD)  
630 signals in 16 motor and non-motor regions of interest for 67 PD patients, from which 62  
631 underwent DBS of the subthalamic nucleus and 5 underwent DBS of the globus pallidus. They  
632 trained a linear discriminant analysis algorithm on normalized BOLD changes using 5-fold  
633 cross-validation and obtained great performance in classifying optimal vs non-optimal  
634 parameter settings, although the performance was lower on two additional (a priori clinically  
635 optimized and in stimulation naive patients) unseen data sets.

636         Geraedts and colleagues (67) also investigated deep brain stimulation in the context of  
637 cognitive function, as a downside of DBS for PD is the potential deterioration of cognition  
638 postoperatively. They extracted features from electroencephalograms, trained random forest  
639 algorithms using 10-fold cross-validation, and obtained great discrimination between PD  
640 patients with the best and worst cognitive performances. However, it should be noted that they  
641 only included the best and worst cognitive performers (n=20 per group from 112 PD patients),  
642 making the classification task probably much easier than if it was performed on the 112 PD  
643 patients, thus requiring their model to be evaluated on PD patients independently on their  
644 cognitive performance. Nonetheless, their results suggest the potential utility of  
645 electroencephalography for cognitive profiling in DBS.

### 646 **5.3. Others**

647 Phokaewvarankul and colleagues (68) explored the effect of electrical muscle stimulation as  
648 an adjunctive treatment for resting tremor during “ON” period, with machine learning used to  
649 predict the optimal stimulation level that will yield the longest period of tremor reduction or  
650 tremor reset time. They used sensor data from a glove incorporating a 3-axis gyroscope to

651 measure tremor signals. The stimulation levels were discretized into five ordinary classes, with  
652 the objective to predict the accurate class from the sensor data. They observed a significant  
653 reduction in tremor parameters during stimulation. The best performing machine learning  
654 model was a LSTM neural network in comparison to classic algorithms such as logistic  
655 regression, support vector machine and random forest. The high predictive performance of the  
656 LSTM model confirmed the potential utility of electrical muscle stimulation for reduction of  
657 resting tremors in PD.

658 Panyakaew and colleagues (69) investigated the identification of modifiable risk factors  
659 of falls. The input data consisted of clinical demographics, medications and balanced  
660 confidence scaled by the 16-item Activities-Specific Balance Confidence (ABC-16) scale,  
661 from 305 PD patients (99 fallers, 58 recurrent fallers and 148 non-fallers). They trained two  
662 gradient tree boosting algorithms using 7-fold cross-validation. They obtained good predictive  
663 performance at differentiating fallers from non-fallers, the most relevant features being item 7  
664 (sweeping the floor), item 5 (reaching on tiptoes) and item 12 (walking in a crowded mall)  
665 from the ABC-16 scale, followed by disease stage and duration. They obtained even better  
666 performance at differentiating recurrent fallers from non-fallers, the most relevant features  
667 being items 12, 5 and 10 (walking across a parking lot) from the ABC-16 scale, followed by  
668 disease stage and current age.

## 669 **6. Conclusion**

670 Many research works on Parkinson's disease and related disorders using machine learning have  
671 been published in the literature, investigating diagnosis, symptom severity, disease progression  
672 and personalized therapies. These studies provide new insights to better understand these  
673 neurodegenerative disorders.

674 However, many questions and challenges are still open. The early-stage, and even more  
675 so the prodromal-stage, classification of Parkinson's disease is still very challenging. The early  
676 differential diagnosis of parkinsonian syndromes is another topic for which higher performance  
677 is needed at an early stage. More highly personalized therapies are also needed to better  
678 improve the quality of life of the PD patients. All the research works on these topics also need  
679 to be evaluated in non-research environments in order to be translated to the clinics.

680 Right usage of machine learning is required to try to answer these questions and  
681 challenges. The most common methodological issues are usually related to the cross-validation  
682 procedure used, which can lead to biased, overly optimistic, reported predictive performance.  
683 Nonetheless, our anecdotal experience after performing this literature review is that these issues  
684 are less and less frequent over time. Nonetheless, many studies use small data sets and leave-  
685 one-out cross-validation, which provides an unbiased estimation of the predictive performance,  
686 but with high variance. The few studies that investigated replicating their results in another  
687 independent data set all reported (much) lower predictive performance, highlighting the critical  
688 need of replication. Using artificial intelligence algorithms also rises ethical and legal issues  
689 regarding the collection, processing, storage and reuse of potentially sensitive patient data,  
690 particularly coming from sensor-based digital data (9). These aspects will have to be taken into  
691 consideration when transferring results obtained from clinical research to clinical routine use.

692 To conclude, the use of machine learning has allowed researchers to better understand  
693 Parkinson's disease and related disorders and suggested potential to better diagnose these

694 disorders as well as to provide better care for the patients, but more research works and  
695 replication studies are required to translate these results into the clinics through clinical  
696 decision support systems.

698 **Table 1. Main characteristics of Parkinson's disease and its related disorders**

<b>Disorder</b>	<b>Parkinson's disease</b>	<b>Multiple system atrophy</b>	<b>Progressive supranuclear palsy</b>	<b>Dementia with Lewy bodies</b>	<b>Cortico-basal degeneration</b>
<b>Pathophysiology</b>	Aggregates of $\alpha$ -synuclein in dopaminergic neurons in brainstem	Aggregates of $\alpha$ -synuclein in neurons (cerebellum, pons, basal ganglia) and oligodendrocytes (glial cytoplasmic inclusions)	Aggregates of 4-repeat tau in astrocytes (tufts), oligodendrocytes (coiled bodies) and neurons (neurofibrillary tangles) in basal ganglia and brainstem	Aggregates of $\alpha$ -synuclein in neurons of the neocortex and brainstem	Aggregates of 4-repeat tau in astrocytes (astrocytic plaques), oligodendrocytes (coiled bodies) and neurons (neurofibrils) in neocortex and basal ganglia
<b>Prevalence</b>	100-300/100,000	5/100,000	5-10/100,000	50/100,000	1/100,000
<b>Main symptoms</b>	<ul style="list-style-type: none"> <li>• Levodopa-responsive parkinsonian syndrome</li> <li>• Non-motor symptoms: Dysautonomia, anxiety, depression, sleep disorders, late cognitive dysfunction</li> </ul>	<ul style="list-style-type: none"> <li>• Parkinsonian syndrome with poor response to levodopa</li> <li>• Early and severe dysautonomia, or cerebellar syndrome</li> </ul>	<ul style="list-style-type: none"> <li>• Axial predominant parkinsonian syndrome nonresponsive to levodopa</li> <li>• Early gait disturbance and falls</li> <li>• Supranuclear gaze palsy</li> <li>• Frontal syndrome</li> </ul>	<ul style="list-style-type: none"> <li>• Parkinsonian syndrome responsive to levodopa</li> <li>• Early dementia</li> <li>• Early hallucinations or illusions</li> <li>• Fluctuations in alertness and attention</li> </ul>	<ul style="list-style-type: none"> <li>• Asymmetric parkinsonian syndrome nonresponsive to levodopa</li> <li>• Apraxia and dystonia</li> <li>• Early dementia</li> </ul>
<b>Symptomatic treatment</b>	<ul style="list-style-type: none"> <li>• Levodopa, dopamine agonists, C-dopamine metabolism inhibitors, amantadine</li> <li>• Deep brain stimulation for advanced cases</li> </ul>	<ul style="list-style-type: none"> <li>• Levodopa</li> <li>• Droxidopa, ephedrine, midodrine or fludrocortisone for hypotension</li> </ul>	<ul style="list-style-type: none"> <li>• Levodopa</li> </ul>	<ul style="list-style-type: none"> <li>• Levodopa</li> <li>• Cholinesterase inhibitors</li> </ul>	<ul style="list-style-type: none"> <li>• Levodopa</li> <li>• Botulinum toxin A for treating focal dystonia</li> </ul>



700 **Table 2. Summary of the potential benefits of machine learning for Parkinson’s disease**  
 701 **and related disorders**

<b>Disease stage</b>	<b>Potential benefits</b>
Early PD diagnosis	<ul style="list-style-type: none"> <li>• Better clinical decision support systems</li> <li>• Higher performance than current diagnostic criteria</li> <li>• Better management and improved quality of life</li> <li>• Potential preventive therapeutic strategies</li> </ul>
Differential diagnosis	<ul style="list-style-type: none"> <li>• Better clinical decision support systems</li> <li>• Higher performance than current diagnostic criteria</li> <li>• Better management and improved quality of life</li> </ul>
Symptom detection and quantification	<ul style="list-style-type: none"> <li>• More frequent, more robust assessment of symptoms with automatic analysis of sensor data</li> <li>• Better management and improved quality of life</li> </ul>
Disease progression	<ul style="list-style-type: none"> <li>• Identification of disease subtypes</li> <li>• Prediction of future symptoms</li> <li>• Treatment adjustment for potential prevention</li> </ul>
Treatment adjustment	<ul style="list-style-type: none"> <li>• Better clinical decision support systems</li> <li>• Personalized therapy</li> <li>• Prevention of adverse events</li> <li>• Better management and improved quality of life</li> </ul>

702

703 **Table 3. Summary of the studies reviewed in this chapter.**

Study	Section	Objectives / Tasks	Modalities	Datasets	Number of subjects	Methods
Wahid et al. 2015 (10)	2.1.1	PD diagnosis (PD vs HC)	Motion data (gait)	Local	23 PD, 26 HC	NB, kNN, SVM, RF, KFD
Mirelman et al. 2021 (11)	2.1.1	PD diagnosis (PD vs HC), PD stage classification	Motion data (gait)	Local	100 HC, 58 PD-HYI, 190 PD-HYII, 84 PD-HYIII	RUSBoost
Kostikis et al. 2015 (12)	2.1.1	PD diagnosis (PD vs HC)	Motion data (hand movement)	Local	25 PD, 20 HC	NB, LR, SVM, AdaBoost, DT, RF
Kotsavasiloglou et al. 2017 (13)	2.1.1	PD diagnosis (PD vs HC)	Motion data (hand movement)	Local	24 PD, 20 HC	NB, LR, SVM, AdaBoost
Amato et al. 2021 (14)	2.1.2	PD diagnosis (PD vs HC)	Voice data	IPVC, local	28 PD, 22 HC; 26 PD, 18 HC	NB, kNN, SVM, RF, AdaBoost, gradient boosting, bagging ensemble
Jeancolas et al. 2021 (15)	2.1.2	PD diagnosis (PD vs HC)	Voice data	Local	121 PD, 100 HC	MFCC-GMM, X-Vector
Jeancolas et al. 2022 (16)	2.1.2	PD diagnosis (PD vs HC)	Voice data	Local	117 PD, 41 iRBD, 98 HC	SVM
Quan et al. 2021 (17)	2.1.2	PD diagnosis (PD vs HC)	Voice data	Local	30 PD, 15 HC	DT, kNN, NB, SVM, MLP, LSTM
Adeli et al. 2016 (21)	2.1.3	PD diagnosis (PD vs HC)	Imaging data (MRI)	PPMI	374 PD, 169 NC	JFSS+Robust LDA
Solana-Lavalle and Rosas-Romero 2021 (22)	2.1.3	PD diagnosis (PD vs HC)	Imaging data (MRI)	PPMI	114 PD, 49 HC; 234 PD; 110 HC	kNN, SVM, RF, NB, LR, MLP, BNN
Mudali et al. 2015 (23)	2.1.3	PD diagnosis (PD vs HC), differential diagnosis	Imaging data (FDG-PET)	Local	20 PD, 21 MSA, 17 PSP, 18 HC	DT
Huppertz et al. 2016 (26)	2.2	Differential diagnosis	Imaging data (MRI)	Local	204 PD, 106 PSP, 21 MSA-C, 60 MSA-P, 73 HC	SVM
Archer et al. 2019 (27)	2.2	Differential diagnosis	Imaging data (MRI)	Local	511 PD, 84 MSA, 129 PSP, 278 HC	SVM
Chougar et al. 2021 (28)	2.2	Differential diagnosis	Imaging data (MRI)	Local	63 PD, 21 PSP, 11 MSA-P, 12 MSA-C, 72 HC; 56	LR, SVM, RF

					PD, 30 PSP, 24 MSA-P, 11 MSA-C, 22 HC	
Shinde et al. 2019 (29)	2.2	Differential diagnosis	Imaging data (MRI)	Local	45 PD, 20 APS, 35 HC	CNN, Gradient boosting
Jucaite et al. 2022 (30)	2.2	Differential diagnosis	Imaging data (PET)	Local	24 PD, 66 MSA	LDA
Khawaldeh et al. 2020 (31)	2.3	Parkinson's disease understanding (subthalamic nucleus activity)	Signal data (LFP)	Local	18 PD	NB
Poston et al. 2016 (32)	2.3	Parkinson's disease understanding (cognition)	Imaging data (fMRI)	Local	54 PD	SVM
Trezzi et al. 2017 (33)	2.3	Parkinson's disease understanding (metabolism)	CSF	Local	44 PD, 43 HC	LR
Vanneste et al. 2018 (34)	2.3	Parkinson's disease understanding (thalamocortical dysrhythmia)	Signal data (rs-EEG)	Local	31 PD, 264 HC, 153 tinnitus, 78 CP, 15 MDD	SVM
Ahlich et al. 2016 (37)	3.1	Symptom detection and quantification (freezing of gait)	Motion data (gait)	Local	20 PD (8 with FOG, 12 without FOG)	SVM
Aich et al. 2018 (38)	3.1	Symptom detection and quantification (freezing of gait)	Motion data (gait)	Local	51 PD (36 with FOG, 15 without FOG)	SVM, kNN, DT, NB
Borzi et al. 2021 (39)	3.1	Symptom detection and quantification (freezing of gait)	Motion data (gait)	Local	11 PD	SVM, kNN, LDA, LR
Dvorani et al. 2021 (40)	3.1	Symptom detection and quantification (freezing of gait)	Motion data (gait)	Local	16 PD	SVM, AdaBoost
Park et al. 2021 (42)	3.2	Symptom detection and quantification (bradykinesia and tremor)	Motion data (resting tremor and finger tapping)	Local	55 PD	SVM
Kim et al. 2018 (43)	3.2	Symptom detection and quantification (tremor)	Motion data (tremor)	Local	92 PD	CNN, RF, NB, LR, DT, SVM, MLP
Eskofier et al. 2016 (44)	3.2	Symptom detection and quantification (bradykinesia)	Motion data (motor tasks)	Local	10 PD	CNN, AdaBoost, kNN, SVM
Abós et al. 2017 (46)	3.3	Symptom detection and quantification (cognition)	Imaging data (rs-fMRI)	Local	27 PD-MCI, 43 PD-CN, 38 HC	SVM
Betrouni et al. 2019 (47)	3.3	Symptom detection and quantification (cognition)	Signal data (EEG)	Local	118 PD	SVM, kNN

García et al. 2021 (48)	3.3	Symptom detection and quantification (cognition)	Voice data	Local	40 PD, 40 HC	SVM, AdaBoost
Morales et al. 2013 (49)	3.3	Symptom detection and quantification (cognition)	Imaging data (MRI)	Local	16 PD-CN, 15 PD-MCI, 14 PD-D	NB, SVM
Shibata et al. 2022 (50)	3.3	Symptom detection and quantification (cognition)	Imaging data (MRI)	Local	61 PD-MCI, 59 PD-CN	RF, gradient boosting, light gradient boosting
Hannink et al 2017 (51)	3.4	Symptom detection and quantification (gait)	Motion data (gait)	eGaIT	99 geriatric subjects	CNN
Lu et al. 2021 (52)	3.4	Symptom detection and quantification (gait)	Motion data (gait)	Local	55 PD	CNN
Gao et al. 2018 (53)	3.4	Symptom detection and quantification (falls)	Clinical data (motor exams)	Local	148 PD (45 fallers, 97 non-fallers); 103 PD (41 fallers, 62 non-fallers)	LR, SVM, RF, gradient boosting
Severson et al. 2021 (54)	4.1	Disease progression (disease states)	Clinical data	PPMI, local	423 PD, 196 HC; 610 PD	HMM
Salmanpour et al. 2022 (55)	4.1	Disease progression (disease trajectories)	Clinical and imaging (MRI) data	PPMI	885 PD	k-means
Oxtoby et al. 2021 (56)	4.2	Disease progression (prediction of sequence of events)	Clinical and genetic data	Local, PPMI	100 PD, 33 HC; 350 PD, 127 HC	Event-based model
Latourelle et al. 2017 (57)	4.2	Disease progression (prediction of motor progression)	Clinical and genetic data	PPMI, local	312 PD, 117 HC; 317 PD	REFS
Ahmadi Tastegar et al. 2019 (58)	4.2	Disease progression (prediction of motor and non-motor symptoms)	Clinical data and inflammatory cytokine measurements	LRRK2 Cohort Consortium	80 iPD, 80 PD-LRRK2	Elastic-net, RF
Amara et al. 2017 (59)	4.2	Disease progression (prediction of excessive daytime sleepiness)	Clinical and imaging (DaTscan) data	PPMI	423 PD, 196 HC	Random survival forest
Couronné et al. 2019 (60)	4.2	Disease progression (prediction of motor and non-motor symptoms)	Clinical and imaging (DaTscan) data	PPMI	362 PD	Generative mixed effect model
Faouzi et al. 2022 (61)	4.2	Disease progression (prediction of impulse control disorders)	Clinical and genetic data	PPMI, local	380 PD; 388 PD	LR, SVM, RF, gradient boosting, RNN

Yang et al. 2021 (63)	5.1	Treatment adjustment (motor symptoms)	Imaging data (fMRI)	Local	38 PD	Ridge, SVM, AdaBoost, gradient boosting
Kim et al. 2021 (64)	5.1	Treatment adjustment (motor symptoms)	Clinical and medication data	PPMI	431 PD	Markov decision process
Boutet et al. 2021 (66)	5.2	Optimal deep brain stimulation parameters	Imaging data (fMRI)	Local	67 PD	LDA
Geraedts et al. 2021 (67)	5.2	Optimal deep brain stimulation parameters	Signal data (EEG)	Local	112 PD	RF
Phokaewvarangkul et al. 2021 (68)	5.3	Electrical muscle stimulation (resting tremor)	Motion data (hand tremor)	Local	20 PD	LR, RF, SVM, MLP, LSTM
Panyakaew et al. 2021 (69)	5.3	Adverse event prevention (identification of modifiable risk factors of falls)	Clinical data	Local	305 PD	Gradient boosting

704

705 **Modalities:** CSF, cerebrospinal fluid; DaTscan, dopamine transporter scan; EEG, electroencephalography; FDG-PET, [18F]-fluorodeoxyglucose positron  
706 emission tomography; fMRI, functional magnetic resonance imaging; LFP, local field potential; MRI, magnetic resonance imaging; PET, positron emission  
707 tomography; rs-EEG, resting-state electroencephalography; rs-fMRI, resting-state functional magnetic resonance imaging.

708

709 **Datasets:** eGaIT, embedded Gait analysis using Intelligent Technologies (<https://www.mad.tf.fau.de/research/activitynet/digital-biobank/>); IPVC, Italian  
710 Parkinson's Voice and Speech (<https://iee-dataport.org/open-access/italian-parkinsons-voice-and-speech/>); LRRK2 Cohort Consortium  
711 (<https://www.michaeljfox.org/news/lrrk2-cohort-consortium/>); PPMI, Parkinson's Progression Markers Initiative (<https://www.ppmi-info.org/>).

712

713 **Subjects:** APS, atypical parkinsonian syndromes; CP, chronic pain; FOG, freezing of gait; HC, healthy controls; iPD, idiopathic Parkinson's disease; iRBD,  
714 idiopathic rapid eye movement sleep behavior disorder; MDD, major depressive disorder; MSA, multiple system atrophy; MSA-C, cerebellar variant of multiple  
715 system atrophy; MSA-P, parkinsonian variant of multiple system atrophy; PD, Parkinson's disease; PD-CN, Parkinson's disease with normal cognition; PD-D,  
716 Parkinson's disease with dementia; PD-HYI, Parkinson's disease with Hoehn & Yahr stage 1; PD-HYII, Parkinson's disease with Hoehn & Yahr stage 2; PD-  
717 HYIII, Parkinson's disease with Hoehn & Yahr stage 3; PD-LRRK2, Parkinson's disease with LRRK2 mutation; PD-MCI, Parkinson's disease with mild  
718 cognitive impairment; PSP, progressive supranuclear palsy.

719

720 **Methods:** BNN, Bayesian neural network; CNN, convolutional neural network; DT, decision tree; HMM, hidden Markov model; JFSS, joint feature-sample  
721 selection; KFD, kernel Fisher discriminant; kNN, k-nearest neighbors; LR, logistic regression; LDA, linear discriminant analysis; LSTM, long short-term  
722 memory; MFCC-GMM, Mel-frequency cepstral coefficients - Gaussian mixture model; MLP, multi-layer perceptron; NB, naive Bayes; REFS, reverse

723 engineering and forward simulation; RF, random forest; RNN, recurrent neural network; RUSBoost, random under-sampling boosting; SVM, support vector  
724 machine.

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