Parkinson's disease and its subtypes

A research paper on describing the heterogeneity of the disease and its subtypes

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Abstract:

Parkinson's disease (PD) is known to be a clinical heterogeneous disease[65], and there has been relatively few useful studies that tried to subtype it in order to help in estimating its prognosis and the length of its progression.
Studying this disease as a whole, has made it difficult in explaining why some patients have particular symptoms and other patients have different ones. and also why some patients experience rather more aggressive pattern of PD, and some other experience milder form.
In this project assignment, I have tried to present the Parkinson's disease with its wide variety of symptoms and how dividing them and the disease's pathophysiology into subtypes would help in better understanding it.
With successfully subtypng PD, it would be easier to treat the symptoms, precisely predict its prognosis and better understand its pathophysiology.
I have also tried to discuss - based on recent studies - what criteria the future studies, on PD subtyping, should use to better map the disease.

Keywords: Parkinson’s disease – Subtypes – Lewy bodies – Cluster analysis – Heterogeneous – Tremor-dominant – PIGD – Substantia Nigra – Basal Ganglia.

Sammendrag:

Parkinsons sykdom (PD) er kjent for å være en klinisk heterogen sykdom, og det har vært relativt få nyttige studier som har forsøkt å subtype den, fordi den vil hjelpe til med å estimere prognosen og lengden på progresjonen.
Å studere denne sykdommen som helhet har gjort det vanskelig å forklare hvorfor noen pasienter har spesielle symptomer og andre pasienter har forskjellige. Også hvorfor noen pasienter opplever ganske mer aggressivt mønster av PD, og andre opplever mildere form.
I denne prosjektoppgaven har jeg prøvd å presentere Parkinsons sykdom med dens brede utvalg av symptomer og hvordan inndeling av dem og sykdommens patofysiologi i undertyper vil hjelpe til med å finne en relevans mellom sykdommens lengde og hvilke symptomer som vises.
Med vellykket undertrykkelse av PD, ville det være lettere å behandle symptomene, presist forutsi prognosen og bedre forstå patofysiologien.
Jeg har også prøvd å foreslå hvilke kriterier fremtidige studier, på PD-undertyping, skal bruke for å kartlegge sykdommen bedre.

Preface:

Like any neurological disease, I have been fascinated by how complicated neurological disorders are. Starting from the human brain, there’s so much we know about it, and yet so much we haven’t discovered yet. From my personal experience, I always believed that the most precious part of the human being is the brain, and I also felt that brain disease is the most what a person can struggle with, because it’s the main part of what we are.
During the neurology semester, Parkinson’s disease has been one of my favorite diseases to read about. I had many questions about why it’s so diverse, and how this pathogen of so called, amyloid plaques, could affect so many areas in the brain and how that could affect the patient clinically. One of the reasons I decided to write about Parkinson’s disease, is after I observed its patients and the extent of distress they experience emotionally and physically.

In this assignment, I'd like to present PD in its diverse aspects as a neuro-degenerative, progressive and varied symptoms, with emphasis on other symptoms than the tremor, bradykinesia, gait instability and rigidity.
I'd also like to present some of the many studies done to classify this disease into subtypes due to its heterogeneity, and point out the importance of analyzing the other symptoms.

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INTRODUCTION:

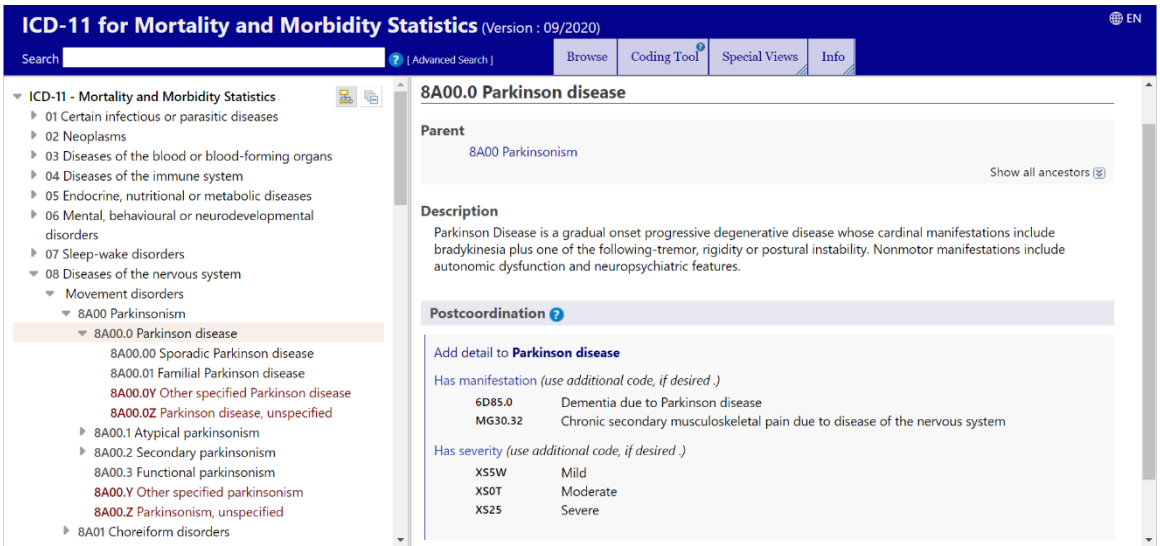
Parkinson's disease (PD) is a chronic, progressive neurodegenerative disorder characterized by bradykinesia, tremor, rigidity and postural instability.

PD dates back to Egyptian and ancient times describing patients with similar motor symptoms [(10)]. In 1817, James Parkinson described the disease with its combined motor symptoms in his essay: An Essay on the Shaking Palsy [(11)]. Other milestones in PD history include Jean-Martin Charcot's collaboration between 1868 and 1881[(12)]. He described several other Parkinson features as mask face and akathisia and he suggested to name the disorder Parkinson's disease. Fredric Lewy discovered Lewy bodies in 1912[(12)] which is the pathological hallmark of PD. Alpha-synuclein protein, the main constitute of Lewy bodies was identified in 1997[(14)].

The main cause of disease is lack of neurotransmitter dopamine was confirmed in the 1950's ([13)] by Ehringer and Hornykiewicz. The first report of effective levodopa therapy was established in 1967 which is still the main therapy for PD [(13)]. Deep Brain Stimulation (DBS) is a treatment opportunity in advanced PD and it became as a possible treatment in the 1980's ([15)].

PD is the second most common neurodegenerative disease and currently, it affects between 7 and 10 million people worldwide [(9)]. Approximately 1-2% of the population aged over 65 years develop PD. Average age of onset is around age 70 however it might occur at younger age as well. Few studies report that women are more often affected by PD[(5)], although most of the studies suggest that men are 1.5 times more likely to have PD compared to women[(9)].

PD is a heterogeneous disorder based on wide clinical spectrum. To this date, the ICD-11 hasn't enlisted any PD subtypes.



Source: https://icd.who.int/browse11/l-m/en#/http%3a%2f%2fid.who.int%2ficd%2fentity%2f296066191

The cause of PD is still unknown, although 1-5% of all PD might be inherited. The most common genetic mutation is localized in the LRRK2 gene [(46)]. Environmental factors also play an important role in developing PD [(5)]. The main risk factor to develop PD is increasing age.

PD is a chronic neurodegenerative disorder caused by the depletion of the neurotransmitter dopamine in the neurons localized in the basal ganglia called substantia nigra.
The basal ganglia is responsible primarily for motor control, as well as motor learning, executive functions, behaviors and emotions [48].

Dopaminergic denervation of the striatum, which in turn induces a demodulation of complex motor circuits comprising the motor and premotor cortices, the putamen, the Globus pallidum, the subthalamic nucleus, and the thalamus[1]. Thus the striato-cerebello-thalamic pathways become disturbed [2]. When the first motor signs of PD appears, about 60-80% of the dopaminergic neurons in substantia nigra have already been lost.

Due to unknown mechanism, the alpha-synuclein protein becomes misfolded and accumulates into Lewy Bodies and is assumed cytotoxic [6]. A study from 1999 defines Lewy bodies as composed of hyper phosphorylated neurofilament proteins, lipids, redox-active iron, ubiquitin, and α-synuclein. α-synuclein, is usually unfolded in α-helical form. By gene mutation, environmental stress or other factors it can be transformed to β-folding which is sensible to self-aggregation in filamentous fibrils and formation of insoluble intracellular inclusions that may lead to functional disturbances and, finally, to death of the involved neurons [7]. According to Braak staging the spreading of Lewy body pathology starts in the olfactory bulb, and continues cranially to the medulla and then the midbrain where the basal ganglia is located[8]. Braak staging is explained in details in nonmotor subtyping.

As a result of the dopamine reduction, the patient experiences the classical cardinal motor symptoms like: **tremor**, usually at rest with back and forth movements. **Rigidity**, the muscles get contracted and become stiff and resistant to movement. Usually, the patient's face become less mimic or emotionless. **Bradykinesia** is slowness of movements. And the last of the cardinal symptoms of PD is **postural instability** which can lead to increased risk of falls[3]. Other non-motor symptoms are also often present like apathy, depression, constipation, sleep and behavior disorders, loss of sense of smell and cognitive impairment.

There's no cure for PD to this date, but medications might improve the motor symptoms. Levodopa is a dopamine substitute with good effect on the motor symptoms. Levodopa is combined by carbidopa to reduce levodopa's side effects and help levodopa to cross the blood-brain-barrier. COMT inhibitors might be used in combination with levodopa for wearing off phenomena, which is when the symptoms come back or worsen before the next dose of Levodopa is taken. Dopamine agonists and MAO-B inhibitors might also be effective in the medical treatment.

PD is still a clinical diagnosis which is based on medical history and neurological examination with presence of classical motor symptoms. Although definite diagnosis is made by post-mortem autopsy findings based on loss of dopaminergic cells in substantia nigra and presence of Lewy bodies.
It's important to exclude other possible reasons for these symptoms like stroke, use of antipsychiatry drugs. Imaging by MRI might help us to exclude other secondary etiology. MRI of brain in PD patients is normal. DatScan imaging might help us to support diagnosis by reduced uptake but it is an unspecific examination and might be positive by other neurodegenerative disorders as well. In the clinical practice other supportive criteria is used as unilateral symptoms in the early phase but the best confirming of the diagnosis is excellent response to levodopa. Other imaging techniques have been used for PD patients as diffusion MRI, PET using different tracers, Neuromelanin-MRI with its sensitivity of 89% and specificity of 83%[16], however these are not used in everyday clinical basis.

There are developed several standardized international scales to follow-up patients regarding both motor and non-motor symptoms. The Unified Parkinson's disease rating scale (UPDRS) and the modified version MDS-UPDRS is the most common screening tool. The MDS-UPDRS has four parts: Part I (non-motor experiences of daily living), Part II (motor experiences of daily living), Part III (motor examination) and Part IV (motor complications) [17]. By filling out these scores, it gives a nice overview about daily living difficulties and a standardized examination which also gives opportunity to compare status after changing medical treatment.

Hoehn and Yahr scale was established earlier and is a grading from stage 1 to 5. It gives an impression about disease course and severity. In early disease stage the symptoms are most unilateral but later on they spread to other body parts and involves balance and gait function.

Montreal Cognitive Assessment (MoCA) is a test to assess the cognitive function and has been more common to use in PD patients [18]. There exists several scales to map non-motor symptoms and quality of life as well.

The clinical symptoms in PD patients are various and show a wide spectrum of coexisting non-motor symptoms. The last 30 years numerous studies attempted to describe different types of PD based on motor- and non-motor symptoms and progression rate. Here I present a short overview on subtypes of PD.

METHODS

In this project, I have searched for studies that tried to classify PD into categories. Specifically in the last 10-15 years.
The search was made mainly via NCBI/PMC and PubMed database, with word search like Parkinson’s disease AND non-motor, Parkinson’s disease AND motor and Parkinson’s disease AND subtypes.
The search results were reviews, cohort studies and research papers.
The studies in focus were mostly cluster analysis, and some of them had follow-ups for up to 5 years.
The articles were sorted based on the categorization of PD subtypes.
Gathering these studies I've found, I tried to examine which of the methods that were used in them were more suitable for subtyping PD. For example, which symptoms tend to present together or which ones appear in more mild or severe pattern of the disease.
Reflecting upon these studies, I have also discussed which of their results that succeeded in finding subtypes that are different from each other.

RESULTS:

Few research studies [23] tried to categorize patients into subtypes using cluster analysis, based on combination or grouping (clustering) of different variables like symptoms, age at onset and medication response. They have been used as a model for further research. In the last two decades, there have been fewer studies using these models. Different progression rates have also been used for PD subtypes combined with motor symptoms and presence of cognitive decline. [24]
Several subtypes have been described based on clinical features like motor and non-motor symptoms, age at disease onset and rate of progression to establish as homogeneous groups as

possible. Subtyping could be based on the presence of tremor or a more akinetic-rigid type of disease, also called Postural Instability and Gait Difficulty (PIGD) [66]. Some studies focus on whether dementia is present or not [37] [38] [39]. Many studies combine several subtypes like tremor/dominant, which is slowly progressive disease presenting mostly in earlier age and rarely develops cognitive decline [58] and might have better response to medication. Other parameters like blood and CSF markers, imaging and pathological findings are also described [36].
Other studies have discussed whether atrophy of certain areas in the brain could relate to certain subtype [51]. Another cohort study discussed whether glucose levels were different according to dopamine depletion in PD patients [55].
Homogeneous groups might serve as a target to involve patients into different studies to map the underlying pathology for better understanding basal disease mechanism.

Many of these subtypes are going to be discussed in this research in hope to develop personalized medicine in the future for better prognosis.

THE USE OF CLUSTER ANALYSIS:

In studying PD subtyping, it seems clear that cluster analysis is a type of methodology used in many studies. Cluster analysis is the task of putting a set of groups in such a way that objects in the same group (called a cluster) are more similar (in some sense) to each other than to those in other groups (clusters). Such groups or clusters may be used as basis for sub classification. Importantly, cluster analysis is an objective statistical method aiming to explore and describe relationships between variables without preformed biases or subjective ideas regarding which relationships and variables that are important for describing variants of the disease.

By comparing cluster analysis results using different aspects (clinical, pharmacological, pathological etc.) of PD, they may be mapped to each other and give a better understanding of what contributes to different PD phenotypes.

SUBTYPES BASED ON MOTOR SYMPTOMS:

The two main subtypes are based on motor symptoms whether the patients have tremor or a type with more akinesia and rigidity. They're also called "classical" subtypes. Tremor-dominant presents with tremor at rest but with milder form of postural instability and gait difficulty (PIGD) [66]. PIGD is a form where a patient has no tremor and the symptoms are dominated by slowness of movements, rigidity and parkinsonian gait characterized by a stooped posture, decreased arm swing, and shuffling gait [57].

Earlier studies documented in a large patient-sample that patients who had higher scores in postural instability, gait difficulty more often had cognitive impairment and a faster rate of progression. Tremor-dominant patients had a milder form of these symptoms and a slower rate of progression [58].

Neuro-pharmacologically based studies have reported higher dopamine levels in tremor-dominant PD compared to akinetic-rigid and mixed subtype [27].
Looking at neuropathology, tremor-dominant PD has greater cell loss particularly in the medial part of Substantia Nigra pars compacta, whereas Akinetic-rigid PD has more cell loss in the ventrolateral part of substantia nigra pars compacta [28].

A clinico-pathological study in 2009, found that PIGD subtype had a significantly higher mean pathological grading of cortical Lewy bodies and more cortical amyloid-b plaque load and cerebral amyloid angiopathy than early disease onset and tremor dominant groups [25].
The picture below shows the clusters that were studied along with the portions of Lewy bodies accumulated in the brains of the patients of each subtype.

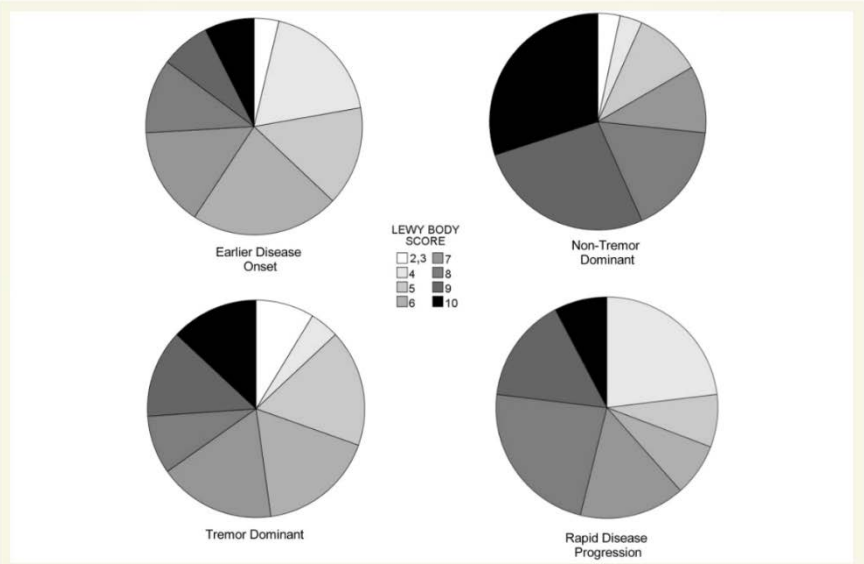


Figure 1 Lewy body scores according to clinical subtypes.

Source: https://pubmed.ncbi.nlm.nih.gov/19759203/

An imaging study from 2013[51] used Voxel Based-Morphometry (VBM), which is a computational approach to neuroanatomy that measures focal differences in brain tissue structure, on 110 patients with idiopathic PD to distinguish differences in gray matter atrophy in specific brain regions. Changes in cortical regions like pre-Supplementary Motor Area (SMA) and Primary Motor Area are related to motor symptoms in PD patients as well as changes in some subcortical regions like the caudate and putamen. The study divided the patients into the two classical motor subtypes of PD, PIGD and TD.
The results showed significant reduction of gray matter in cortical and sub-cortical regions in PIGD patients compared to TD patients.
The study also analyzed the connectivity between different regions in the brain and found that the connection between the pre-SMA and the putamen in PIGD patients was reduced compared with TD patients where the reduction was not seen.
It is worth noting that the study also conducted VBM on two severity-based clusters; the first one is pre-PIGD and pre-TD where patients had milder form of symptoms than in the second cluster, PIGD and TD patients. The grey matter volume in the regions specific to PIGD and

TD showed increased atrophy compared to pre-PIGD and pre-TD. The VBM analyses were adjusted for age, sex and disease duration.
The study also found a correlation between the findings of gray matter atrophy and the clinical symptoms. The PIGD patients mainly have problems with movement initiation, and the center responsible for that is the pre-SMA area in the cortex. And imaging showed that PIGD patients have gray matter atrophy in that area which supports the initiation difficulties. Another main symptom PIGD patients have is gait difficulty. Imaging has shown gray matter atrophy in the Declive and Culmen in the Cerebellum in those patients. Cerebellum is known to be responsible for balance and coordination, and therefore the gait difficulty is most likely caused by the atrophy in the Cerebellum. All these findings strongly support the use of the motor subtypes for future PD studies.

A study from 2012 used FP.CIT.SPECT scan, for Dopamine transporter binding imaging in vivo, on 27 PD patients [52]. FP.CIT is a radiolabel for brain dopamine transporter (DAT) that is useful for the differential diagnosis of Parkinson disease (PD) and other diseases that mimic PD [67].
The patients were divided into 2 subgroups; the classic tremor-dominant and akinetic-rigid. They were matched for age, sex, disease duration severity and levodopa equivalent daily dose (LEDD). So those factors weren't significantly different. Factors like comorbidity were excluded because they would affect the pattern of progression in the FP.CIT.SPECT images. Both imaging and clinical rating by UPDRS III were performed in patients at baseline and at follow up after ca. 2.5 years.
Imaging studies show different dopaminergic depletion in the two PD subtypes.
In tremor-dominant patients was an eagle-wing-shaped while in akinetic-rigid patients was egg-shaped striatal pattern. After a mean follow-up period of 2.5 years akinetic-rigid patients showed a distinct progression of clinical markers and dopaminergic deficit in FP.CIT-scans. The progression of dopaminergic loss was most explicit in the putamen bilaterally. Affection of both putamina in the akinetic-rigid patients might point out a more ‘‘malign’’ course of the disease and could than serve as an indicator for faster progression.
In previous clinical observations, it has been noted that patients with akinetic-rigid subtype show a faster clinical progression and more severe cognitive decline as well as increased dopamine loss in pallidal and striatal areas compared to tremor-dominant PD patients.

In another imaging study [31], using Diffusion Tensor Imaging (DTI) in 21 PD patients and control group of 20 healthy individuals. It aimed at differentiating the two motor subtypes based on significant changes not only in substantia nigra but also Globus pallidus, putamen and caudate bilaterally.

Diffusion-Tensor imaging (DTI) is a form of Diffusion-MR imaging based upon measuring the motion of water molecules within tissue that has fibers like the axons. In general simplified terms, highly cellular tissues or those with cellular swelling exhibit lower diffusion coefficients.

DTI was able to differentiate PD from control groups based on significant changes in subcortical regions [32] [33].
The study found that DTI results were more correlated with UPDRS scores within the PIGD subgroup than TD. The DTI results however, weren't correlated with the disease duration but with the stage of the disease.
The figure below shows significant differences driven by the PIGD subtype and no significant differences were seen between TD patients and controls:

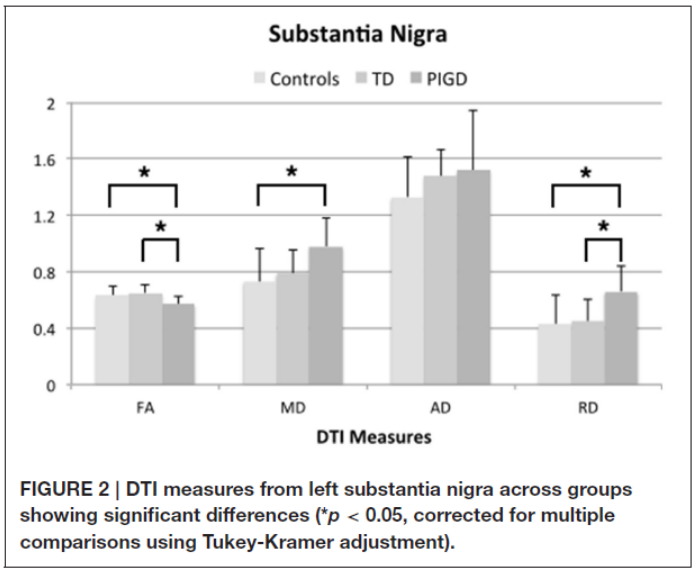


FIGURE 2 | DTI measures from left substantia nigra across groups showing significant differences (*$p < 0.05$, corrected for multiple comparisons using Tukey-Kramer adjustment).

Source: https://www.frontiersin.org/articles/10.3389/fnana.2016.00017/full

A study in 2014[55], was conducted on 64 PD patients grouped into tremor-dominant and akinetic-rigid subtypes to find difference in neuronal consumption of glucose associated with dopamine loss between the two subtypes.
The study used [18F]-fluorodeoxyglucose (FDG) and [18F]-fluoro-L-dopa (F-dopa) PET scans in striatal areas (Putamen + Caudate).
The patients were matched in age, disease duration, LEDD, Hoehn and Yahr stage, age at onset and gender distribution.
Compared to tremor-dominant, akinetic-rigid PD had lower Glucose metabolism in the striatum which correlated with lower Dopamine uptake.

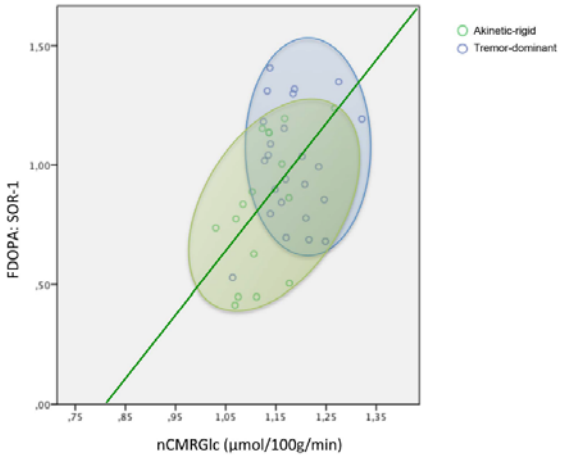


Figure 2. Regional glucose (nCMRGlc) and F-dopa (SOR-1) uptake in a striatal volume of interest identified as subtype-specific for PD patients. The green regression line demonstrates the correlation of nCMRGlc and F-dopa-uptake for akinetic-rigid patients ($r = 0.537$, $p = 0.032$). For methodological considerations see File S1.
dot:10.1371/journal.pone.0096629.g002

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4029550/

SUBTYPES BASED ON NON-MOTOR SYMPTOMS:

Nonmotor symptoms (NMS) are symptoms like neuropsychiatric symptoms, for example, depression and anxiety. Sleep disorders like sleep behavior disorder and insomnia. And autonomic symptoms like bladder disturbances such as urgency and frequency, sweating, orthostatic hypotension and sexual dysfunction [(60)].
NMS may dominate the picture and may appear years before the motor symptoms manifest themselves [(59)]. Therefore such symptoms like for example anxiety and depression, have also been termed prodromal symptoms.

All PD patients have at least one NMS as a 2018 study concluded [(68)]. It analyzed PD patients in Morocco using clinical interview, investigation and universal scales. The result was that the autonomic symptoms (urinary dysfunction) were the most frequent, followed by sleep and psychiatric (depression) disorders. It's been also observed that NMS are more common in non-tremor PD patients than tremor-dominant ones. [(61)(62)(63)]

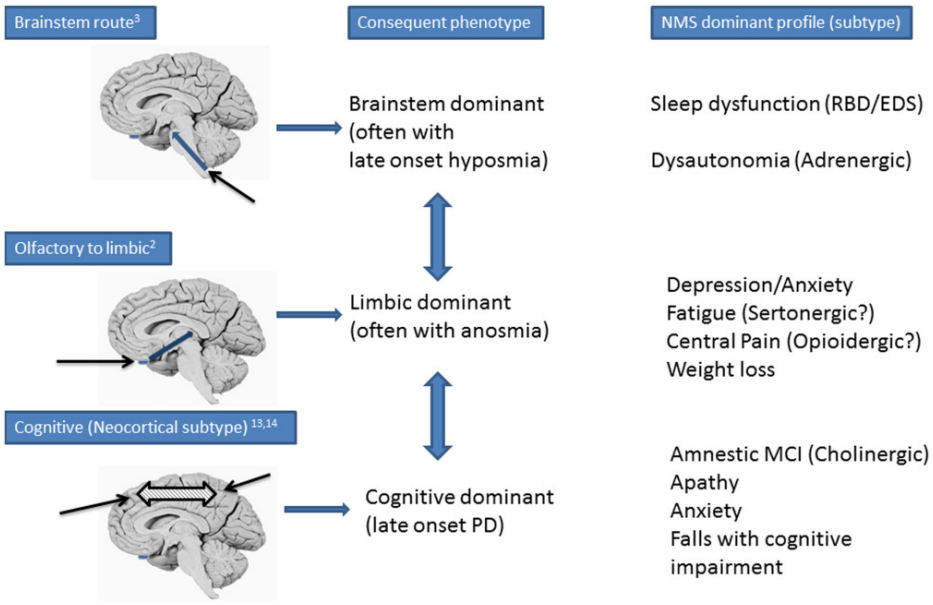
Unfortunately, nonmotor symptoms in PD have not previously been seen as an integral part of PD, although James Parkinson also described them in his treatise. Instead, they have been described as additional symptoms beside the PD classic motor features (tremor, bradykinesia etc.).
One of the reasons may be that it is known that up to 88% of aging people experience nonmotor symptoms due to normal aging [(69)]. Thus PD itself may not always be a direct cause of nonmotor symptoms seen in PD patients. However, nonmotor symptoms in PD are more severe than nonmotor symptoms due to normal aging [(70)].

NMS may appear in fluctuations that are parallel to the motor fluctuations and may also emerge even when the motor fluctuations are clearly seen. A study showed that 28% of PD patients suffered more from disability caused by their NMS fluctuations, than from disability caused by the motor fluctuations [(71)].

One of the important reasons to why those symptoms must be pointed out and treated is to increase the patient's quality of life. PD patients suffer mostly - beside the motor handicap - from emotional and bodily discomfort, and cognitive impairment [(72)].
In addition, many NMS respond well to medication like for example for depression and sleeping problems, so an awareness by neurologists of the importance of treating NMS and not just the classic PD symptoms may potentially contribute towards improving the quality of life of PD patients. Also, a further focus on NMS in future studies may lead to better ways to diagnose and treat them.

Although the mechanism of NMS in PD is still not well-understood, it may be caused by disturbances in other neurotransmitters than Dopamine, like Serotonin and Noradrenaline [(64)].
The pathological process has been introduced by Braak staging [(73) (74) (75)].
Stage 1 involves degeneration in the olfactory bulb, which clinically manifests as loss of smell. Stage 2 is closely adjacent to stage 1, and is characterized by affection of the lower brainstem. This area is thought to mediate some nonmotor symptoms like sleep homoeostasis, olfaction and other autonomic features. Stage 1 and 2 are thought to be the preclinical phase of PD, where nonmotor symptoms may already show up, because affection of the brainstem

also include the nuclei responsible for Serotonin and Norepinephrine (Raphe nucleus and locus coeruleus respectively).
Stage 3 and 4 is when neuro-degeneration has affected the substantia nigra and the motor symptoms can be observed. Stage 5 and 6 is when the Lewy bodies are aggregated in other limbic structures and the neocortex.



The image explains the possible origins of NMS during the development of PD. For example, it is hypothesized that the pathological process of PD starts at the olfactorian bulb and progresses through the lower brainstem to other areas in the cortex. The lower brainstem is responsible for many features including sleep homeostasis. Thus, when PD patient has sleeping problems, it could be caused by PD's degenerative pathology of that area.
Source: https://movementdisorders.onlinelibrary.wiley.com/doi/full/10.1002/mds.26510

Pathophysiology of some specific NMS:

1. REM-sleep behavior disorder:
One of the sleeping disorders that PD patients experience is REM sleep behavior disorder. It's characterized by patients physically acting out their dreams while asleep because of reduced skeletal muscle atonia during the REM cycle. This may lead to falling from bed or talking during sleeping [(76)].
As mentioned before, this is thought to be due to neuro-degeneration of the lower brainstem.

2. Depression:
Depression has been associated with PD more as a symptom than a reaction towards a person having the disease. It's been correlated with affection of serotoninergic neurotransmission as well as other neurotransmitters [(77)].

3. Cognitive impairment:
Dementia in PD patients is progressive and can develop during up to 15 years of disease period [(78)], and is characterized by visuospatial disturbances and memory problems due to loss

of effect of PD medications like Levodopa [79].
Dementia is associated with reduction of Hippocampus size in PD just like Alzheimer's disease [80] which is more logical to why PD patients have memory problems.

Centering on the NMS in PD and attempting to find subtypes from that point of view, a 2017 study used cluster analysis and studied the interactions of a wide range of PD motor and nonmotor symptoms. It presented a statistical confirmation of the importance of non-motor symptoms in PD and demonstrated that the disease may be sub-classified based on them. Given the importance of NMS for the patients, the authors thus suggested future treatment of the disease should be NMS subtype-based.
By analyzing patients in one cluster of groups based on the severity of symptoms, and another cluster of groups based on the NMS, and then aligning the clusters together, researchers found that NMS like mood/anxiety, sleep/fatigue, cognition, and urinary function can be represented as NMS subtypes with patterns of degeneration of non-dopaminergic neurotransmitters in different places of the brain. This suggested that treatment of PD shouldn't be focused only on depletion of Dopamine in Substantia Nigra, but on other neurotransmitters disturbances in other parts of the brain as well.

A study from 2018[54] used two large cohorts of PD patients to distinguish PD subtypes for better understanding the pathophysiology of the disease and find better treatment strategies for each subtype.
The study used cluster analysis and found 4 clusters based on the Levodopa responsiveness and the motor symptoms severity.
The clusters were:

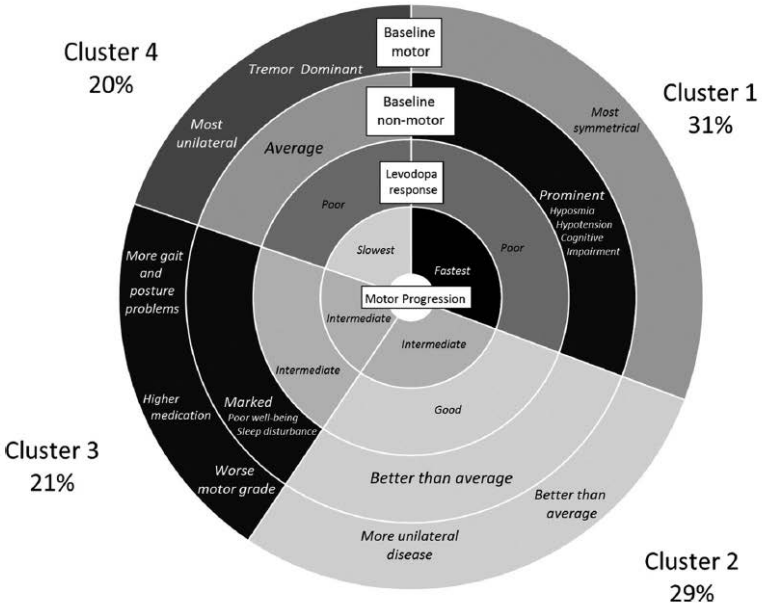


Figure 1 Important salient clinical features of the four clusters across the two cohorts where the percentages within each cluster are from the Tracking Parkinson's cohort.
Source: https://jnnp.bmj.com/content/89/12/1279

The table clarifies what's in the figure about the symptoms, progression and response to Levodopa:

	Cluster (1)	Cluster (2)	Cluster (3) Most severe.	Cluster (4)
Motor	Most symmetrical	More unilateral	More gait and posture problems.	Most unilateral and tremor-dominant.
Non-motor	Hyposmia Hypotension Cognitive impairment	Better than average	Poor wellbeing and sleep disturbance	Average
Levodopa response	Poor	Good	Intermediate (higher medication)	Poor
Motor progression	Fastest	Intermediate	Intermediate	Slowest

Although this study has provided more specific categorization than previous studies, it might be also useful to focus on other non-motor symptoms at the time of the diagnosis. This may help in further stratification of the subtypes at this early disease stage.
Using several scores like UPDRS II, III and MoCA, the patients have been followed up for 3 years to see progression rate. The results showed increased UPDRS III score proportional to the disease severity in each cluster.

SUBTYPES BASED ON COGNITIVE SYMPTOMS:

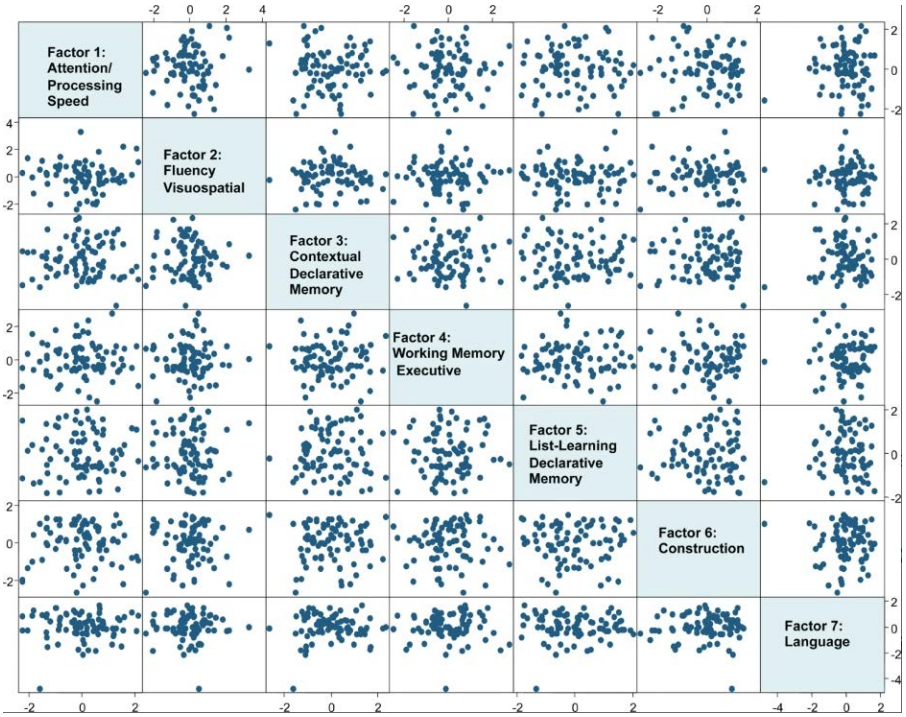
Cognitive impairment has gained large focus related to PD and attempts have been made to categorize patients according to it, even though it falls into the nonmotor category.
Around 30-40% of PD patients suffer from cognitive impairment [(37)].

Cognitive impairment in PD has been classified as PD-MCI (mild cognitive impairment) and PD with dementia (PDD). PD-MCI can become PDD based on severity. The risk increases up to 50% during 5 years. Specific cognitive domains like episodic memory, visuospatial function, semantic fluency, and mental flexibility were more attributed to converting to PDD [(38)].

PD-MCI is further subcategorized into single domain (means one cognitive aspect is affected, like language, visual perception, memory etc.) or multi-domain. The single or multi-domain has been further categorized into amnesic or non-amnesic, therefore there are 4 subtypes [(39)].
The patient is diagnosed with PD-MCI according to consensus Task Force criteria [(40)].
Interestingly, MCI symptoms were reversible in some patients during the follow-up, and symptoms were therefore most likely partly attributed to nervousness, sleep deprivation or stress. In other cases, it was attributed to taking dopaminergic medication and/or to fluctuations [(41)].

MRI studies reported increased frequency of cognitive impairment in patients with PIGD due to atrophy of several brain areas that are responsible for both motor and cognitive functions[42] and they had higher risk of converting into PDD.

A study aimed to examine whether PD patients with cognitive impairment can be classified into subtypes using Task Force guidelines domains [43].
95% of the patients were diagnosed with PD-MCI multi-domain. The domains ranged between memory, language and visual perception.
Upon studying these domains, an analysis was conducted to extract the most important factors from cognitive tests to try and distinguish between PD patients with cognitive impairment. Although seven factors were described, the factors failed to differentiate cognitive PD groups:



Pairs plot of seven factors based on PCFA (principal components factor analysis) of 17 psychometric scores[a] in the PANUC (Pacific Northwest Udall Center) cohort. Matrix of all possible two-dimensional scatterplots for the seven factor scores obtained from PCFA. Each data point represents an individual subject's pair of factor scores (based on the horizontal and vertical axes). Given all possible configurations of pairwise factor scatterplots, there is a **lack of any distinct clustering** of subjects. [a]PCFA was implemented on the standardized residuals from the linear regression of the raw scores adjusted for age at visit, education, disease duration, and sex. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
Source: https://movementdisorders.onlinelibrary.wiley.com/doi/full/10.1002/mds.25875

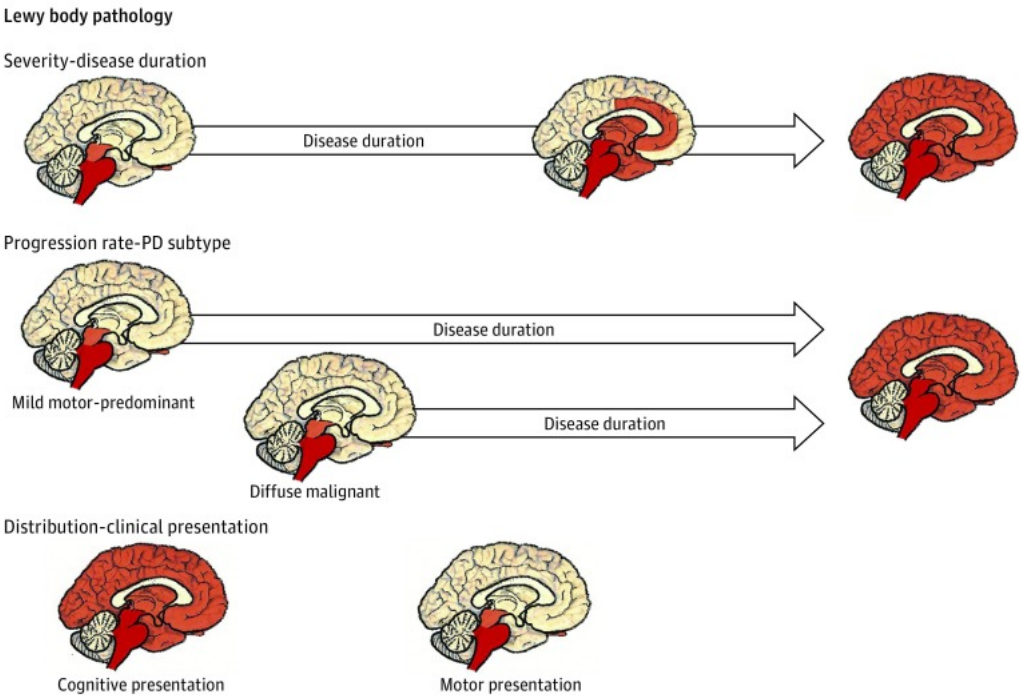
Using cluster analysis, therefore this study concluded that classifying PD into subtypes based on cognitive symptoms or domains only is not sufficient enough. Other factors like motor symptoms, imaging and genetics should be included in future studies to give a better understanding of PD. Also it was suggested to refine the MDS Task Force criteria because of the overlap between the cognitive domains.

SUBTYPES BASED ON PROGRESSION:

In this subchapter, several studies have tried to classify PD into subtypes based on the disease progression. Whether it was early or late onset, the progression was tightly related to the severity of the disease, and it seemed that the earlier the onset, the milder the form of PD. However, the early/late onset is up to debate, because it also depends on how early the disease is diagnosed.

A 2008 study on progression of pathology in PD patients, studied 3 groups of patients; the first group of younger onset patients with typical long clinical course of PD. These patients' autopsy showed lower distribution of Lewy bodies than the other groups. The second group with short disease duration and dementia had severe neocortical Lewy body distribution. The last group had a late disease onset, short course and cognitive decline. This group had the highest Lewy body distribution with amyloid plaques [(26)].

In a retrospective approach, a study in 2019 took a different method for subtyping PD [(50)]. They categorized 111 confirmed PD patients based on their brain autopsy after they died. Factors like motor symptoms, rapid eye movement sleep behavior disorder, and autonomic and cognitive dysfunction were then taken into consideration. Disease milestones (recurrent falls, wheelchair dependence, dementia, and care home placement) and severity and distribution of Lewy pathology and Alzheimer disease–related pathology were assessed as well.
The subtype classification was: mild-motor predominant, intermediate, or diffuse malignant subtypes.
They found that: "the results show that despite a heterogeneous disease course during early-middle stages, advanced stages of the disease are clinically very similar, with accumulation of disability in a similar time course followed by death without any differences on neuropathological findings at post mortem".



Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6459129/

Thus it is important to diagnose the PD patients into subtypes as early as possible, because based on this study, the later the diagnosis, the harder it's going to be to address the right PD subtype because it all becomes similar.

DISCUSSION:

The clusters were mainly groups of patients that had similar symptoms or similar disease duration. The main problem of the subtypes is that there were no subtypes that were completely isolated from each other, and that is one of the main points of discussion in this project.

After presenting the many symptoms and aspects of PD, I am now going to discuss the studies I found that made very important and more comprehensive attempts to categorize PD. these studies relied on all symptoms presented before, progression and severity taken together. More importantly, the transition into clinical application of the proposed subtypes was pointed out as well.

One study included 421 newly diagnosed PD patients [(36)] performed cluster analysis using motor, non-motor, cognitive and autonomic symptoms. A global composite outcome (GCO), was calculated as a single numeric indicator of prognosis. Higher GCO scores represent worse function.
Other criteria like age, biomarkers, demographics and genetics were also taken into consideration.
In order to make this cluster analysis lead into building a future algorithm for PD subtyping and helping in individualized treatment. Symptoms were converted into domains: motor (UPDRS-II, UPDRS-III, and PIGD score), cognition (combining all available neuropsychological batteries in PPMI), RBD (RBDSQ score), and dysautonomia (SCOPA-AUT total score).
Three subtypes were described:
- Subtype I: mild motor-predominant, motor and non-motor symptoms.
- Subtype II: Intermediate, a group of patients that didn't meet the criteria of I or III.
- Subtype III: Diffuse malignant, more severe motor and non-motor symptoms.

The image shows greater atrophy in the diffuse malignant subtype compared to both mild-motor predominant and intermediate subtypes:

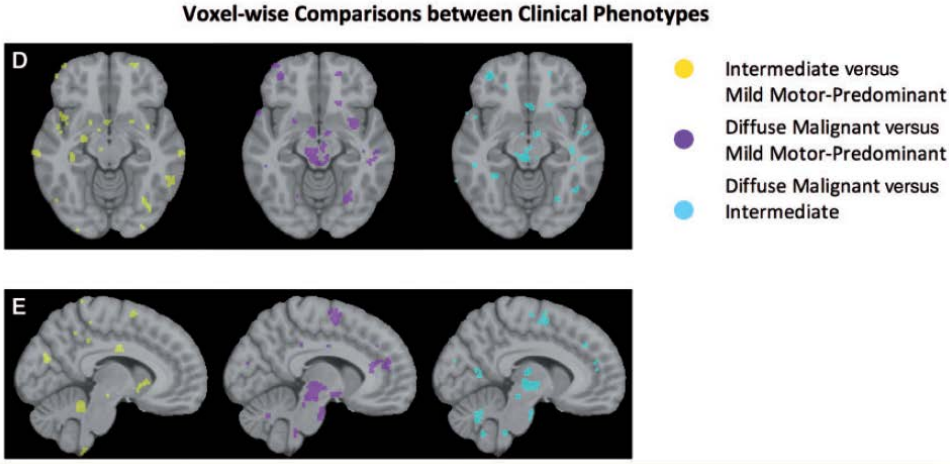
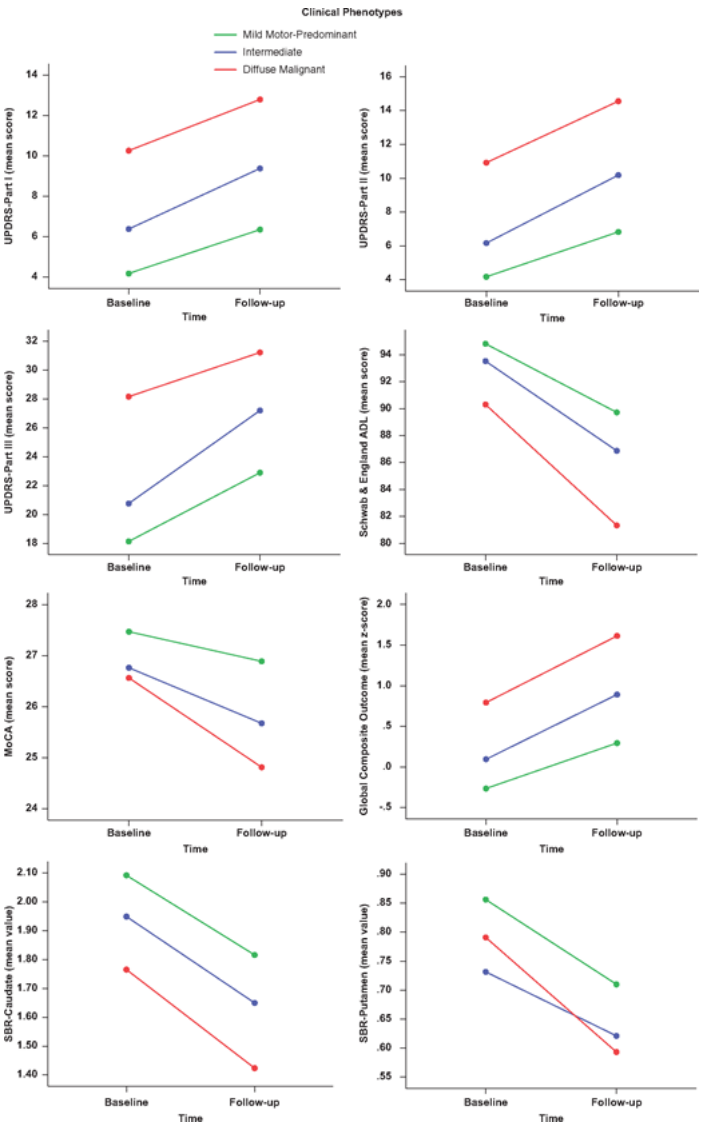


Figure 3 Structural MRI analysis in different clinical phenotypes of Parkinson's disease in the PPMI population. (**D** and **E**) Exploratory comparisons of the whole brain atrophy pattern between clinical subtypes (uncorrected) shows brain areas with higher atrophy in the intermediate subtype compared with the mild motor-predominant subtype (*left*), brain areas with higher atrophy in the diffuse malignant subtype compared with the mild motor-predominant (*middle*) and intermediate (*right*) subtypes.

Source: https://doi.org/10.1093/brain/awx118

In addition, blood, CSF and imaging studies were performed. Surprisingly, there were no significant difference between the three subtypes in Alpha-synuclein levels either in CSF or blood. Dopaminergic SPECT showed lowest denervation in mild-predominant subtype compared to diffuse malignant subtype.
CSF Amyloid-beta was highest in mild-predominant subtype and lowest in diffuse malignant subtype.
At the follow-up (in ca. 2.5 years), it was noticeable that the progression of PD in diffuse malignant and intermediate subtypes was faster than the mild-predominant.

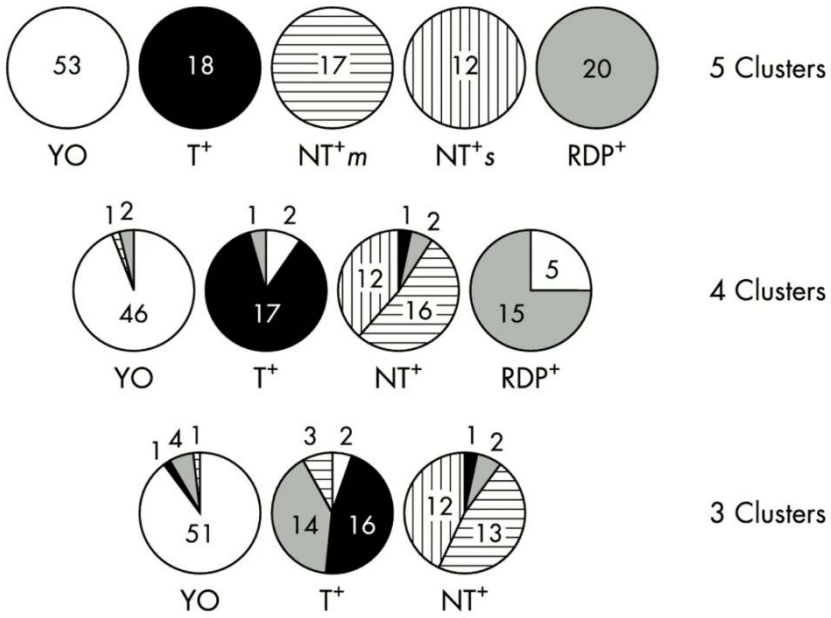


Longitudinal changes in outcomes of interest in different phenotypes of Parkinson's disease in the PPMI (Parkinson's Progression Markers Initiative) population with at least 1 year of follow-up. Patients with diffuse malignant progression scored higher results on different PD assessment scales like MoCA and UPDRS, than patients with mild and intermediate progression.
Source: https://doi.org/10.1093/brain/awx118

This study is unique because it included a large sample size and a wide range of symptoms, criteria, scores and other factors. It was a study that included the PD from almost all its aspects. The result of the 3 clusters was more based on the severity of the disease as a whole and not just focusing on symptoms. That could be the answer to why there hasn't been a complete algorithm of subtyping PD until recent years. Subtyping probably should not be a classification based on one symptom but a combination of several factors. The ultimate goal is not to treat one symptom but all manifestations of the disease itself.

However, there was a significant difference between the clusters and the clinical subtypes, but this approach would encourage for further research to translate information learned from the cluster analysis into clinical subtypes.

The transition from cluster analysis to clinical subtypes should be valid if the subtypes would be reliable every time a patient should be categorized into them and providing the patient doesn't change cluster as disease progresses. For example a cohort study in 2005, tried to find the appropriate PD subtypes in early diagnosed PD patients. The criteria used were demographic, motor, mood, and cognitive factors and symptoms [(44)].
The study used 5 clusters first, 4, and then 3 in order to see if the same patients fell into the same subtype.



Source: https://jnnp.bmj.com/content/76/3/343.full

5 clusters: young onset - tremor dominant - non-tremor dominant with moderate cognitive impairment - non-tremor dominant with severe cognitive impairment and rapid disease progression.
4 clusters: young onset - tremor dominant - non-tremor dominant and rapid disease progression.
3 clusters: young onset - tremor dominant and non-tremor dominant.

Throughout the 3 solutions presented, most of the patients fell into similar categories in every solution, whether it's 5, 4 or 3, with the main divisions being young onset, tremor and non-tremor subtypes. For example, the young onset subtype showed a slow rate of disease progression, mild motor symptoms and no cognitive impairment through all clustering.
Thus the subtypes showed a consistent pattern, and could be strong candidates for PD subtypes in the future. [(44)]

Another study in 2009 gathered 350 PD patients and categorized them into 4 subtypes; rapid disease progression subtype, young-onset subtype, non-tremor-dominant subtype with psychopathology (cognitive impairment, depressive and apathetic symptoms, and hallucinations) and a tremor-dominant subtype.
The aim of the study was to establish different subtypes in a large and diverse sample of PD patients and also to validate the cluster solution by performing a confirmative cluster analysis [(45)]

However, the 4 clusters had significant differences in terms of age, disease duration, Hoehn and Yahr and ADL scores. Thus it had some limitations but, it had high accuracy and validity in terms of classification of PD.

Since PD is highly heterogeneous it is necessary to map out the symptoms, biochemistry, imaging and pathological changes as well as possible. Subtyping of PD according to each symptoms separately won't lead to effective management. However subtyping is important to develop a model including tiers or levels as genetic, pathological and clinical information to build a complete picture of PD. These three tiers would serve as a better model for subtypes. This would help create a better understanding of PD in the future, in hope to individualize treatment [47].

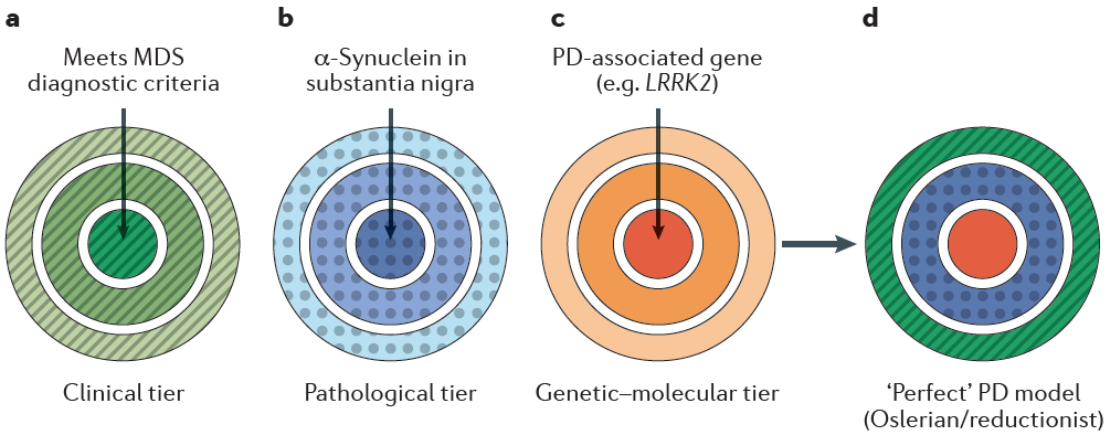


Figure 1 | **Diagnostic tiers of Parkinson disease as single disease.** In this conceptual scheme proposed for research diagnostic criteria[5], three separate **a** | clinical, **b** | pathological, and **c** | genetic–molecular tiers are layered according to high (inner circles) or low (outer circles) likelihood of their convergence to a single Parkinson disease (PD) construct. **d** | A perfect model of PD, according to the tiered cores, would encompass the clinically established MDS criteria for PD, demonstration of α-synuclein pathology, and a PD-causing gene mutation.

Source: https://www.sciencedirect.com/science/article/pii/S1474442213700474?via%3Dihub

This model needs further updates to include disease mechanisms and pathways which are not discovered yet. In the future it would be more interesting to include several biomarkers both biochemical, imaging and genetic for a more detailed and complete picture of the heterogeneous disease picture.

In the preceding studies presented, many have failed to achieve the transition from cluster analysis into clinical subtypes. This is a key problem in finding true PD subtypes, but also a template for future studies in PD, meaning that future research should focus on PD as subtypes and not a single domain.
A 2017 Nature article [46] proposed several recommendations about the transition into clinical subtypes:

- Preserving biological samples from ongoing clinical trials for future analysis using genetic markers, for example.
- The need of separate diagnostic criteria to clinically differentiate PD subtypes. With precise differentiation, it would be easier to discover the different pathological mechanisms for each subtype.
- Ageing should be taken into consideration when developing disease-modifying therapy for PD subtypes, because it may affect the response towards medication depending on the subtype.

- In patient cohorts; vascular, amyloid or other pathologies should be identified, because they would affect the response to disease-modifying treatment.

Although PD has no cure yet, the ability to diagnose PD in its early stage along with identifying correct subtypes, would help in providing the relieving treatment for its symptoms as early as possible and increase the quality of life for the patients.
It is helpful also to detect which areas in the brain have expressed neurodegeneration first, therefore which symptoms the patients is expressing – motor or non-motor. In turn, it would help to easier diagnosis with the proper subtype.

CONCLUSION:

Reviewing Parkinson's disease and examining its subtypes, it has been revealed that PIGD has a faster progression and more severe cognitive impairment than tremor-dominant[58]. tremor-dominant has also less Dopamine depletion than PIGD during the course of the disease[27], although the cell loss differ in which part of the substantia Nigra and other basal ganglia structures between the two subtypes[28][52].
PIGD has more grey matter atrophy in the cortical and sub-cortical regions of the brain compared to tremor-dominant. This atrophy also correlates with the clinical symptoms of PIGD for example initiation of movement and gait difficulties [51] and cognitive impairment [42]. PIGD has also lower Dopamine uptake and lower Glucose metabolism [55] possibly because of more cell loss and more atrophy.
Classifying PD into subtypes based on cognitive impairment has failed, because the proposed clusters/ subtypes weren't differentiated enough from each other [43].
Patients that exhibit PD at a young age experience a milder form of PD with a longer course, opposed to PD patients with late onset and short duration. Those experience a more severe form of Parkinson's disease [26].

Refinement of the clinical classification of PD subtypes is an important goal in PD future research to better understand risk factors, mechanism of disease, underlying genetics, and clinical course, as well as to offer better treatment strategies [31].

Considering studies done on PD subtyping, one might suggest new subtypes from a different perspective. Later studies included several factors in combination. In the future it could be possible to make clusters based on genetic, biochemical and imaging markers since these features might be more related to the underlying causes. Knowledge about the pathological mechanisms would open new opportunities to develop disease-modifying treatment. Other studies focusing also on environmental factors related to specific subtypes like previous head trauma, smoking and geographic occupation may also have a high impact for mapping other important underlying etiologies.[29] [30].

I'd propose an optimal model that describes clusters or groups that future PD patients would be categorized into, based on their symptoms at the time of diagnosis or in other words a predictive model. Such a model could be upgraded with time with increasing knowledge in genetics and different biomarkers into better categorization of the PD patients. This would

help in better understanding of different aspects of PD; its pathophysiology, its course of progression and most importantly the optimal treatment of the different subtypes.

A wider involvement of other factors including etiology and genetic and biomarkers may lead to more individualized and personalized medicine in the aim to offer the most suitable treatment for each patient.

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