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Perspectives of Cognitive Impairment and Behavioral Disturbances in Parkinson's Disease Dementia

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Abstract

Parkinson's disease dementia is a critical stage of the disease because that has a negative impact on the quality of life and functional independence in activities daily living. How the cognition progress to dementia is a key to be explored. The cognitive impairment shows two profiles: cortical (memory encoding, visuospatial abilities, and language) and subcortical, with a dysexecutive syndrome that includes deficits in recognition memory, attention processes, and visual perception as well as visual hallucinations and cognitive fluctuations. Behavioral problems such as apathy, anxiety, depression, and impulse control disorders take a significant part in the loss of autonomy and progression of the disease. To detect the risk of Parkinson's disease dementia development, the integral evaluation of patients in all stages of the disease should consider the interplay of genetic and epigenetic factors, motor subtypes, and non-motor symptoms (NMS) in order to implement different therapeutics and supportive strategies when they are likely to have efficacy.

Keywords: Parkinson's disease, biomarkers, cognitive impairment, dementia, personalized medicine

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide after Alzheimer's disease (AD). Nowadays, PD is considered a pandemic and the projection in the next years exhibited a fast growing of the disease. Estimating the high prevalence of cognitive impairment in the course of the disease, we must encourage the research and increase of health policies to reduce the impact of quality of life and its costs to the health care system.

There is a new and necessary perspective to understand the multicausality of the neurodegenerative diseases that most affect the population. By making available clinical, biological, genetic, and functional brain imaging markers in an individual-centered clinical practice, it will allow an approach to the principle of precision medicine. This can contribute to optimization of the selection of pharmacological

management or non-pharmacological strategies of symptomatic or preventive treatment for cognitive impairment even at early stages of PD. Therefore, identifying patients with potential risk of dementia could guarantee proper treatment and strategies to support the functional impact. We are beginning to understand the conceptual and therapeutic overlap by reclassifying the shared pathogenic mechanisms and therapeutic targets.

The integral and multidisciplinary approach of the motor symptoms (MS) and non-motor symptoms (NMS) through the natural history of the disease allows to provide a specific treatment and improve the quality of life.

2. Epidemiology

PD produces a considerable epidemiological burden associated with high rates of disability [1]. Due to the world population's aging and other unclear factors, PD prevalence and incidence are dramatically increasing, even surpassing the growth of AD [2]. Epidemiological data on PD are highly variable across countries. These differences can be explained by the variability in the diagnostic criteria, changes in population age distribution and the access to health care services, including the opportunity to consult with trained doctors and specialists [3–5].

According to the Global Burden of Disease study, 6.2 million patients live with PD and this frequency will double by 2040. In 2015, the country with the highest age-adjusted PD prevalence was China with 136.34 cases per 100,000 inhabitants (CI 11.56–165.55) and the lowest was Tanzania with 72.19 (CI 59.86–87.82) [5, 6]. Since 1990 until 2017, PD had a small but significant increase in the age-standardized rates of incidence (21.9% [UI, 11.2–14.6%]), prevalence (16.2% [UI, 2.7–31%]), mortality (33.1% [UI, –4.6–41.7%]), and DALY (24.8% [UI, –5.2–32.9%]) [6].

People living with PD often have other comorbidities, which contribute to their prognosis related to the quality of life, and mortality [7]. Xin Wang et al., in a large retrospective study in China, collected and quantified PD comorbidity burden by the Elixhauser Comorbidity Index (ECI) and Charlson Comorbidity Index (CCI). The comorbidity spectrum differed between PD and parkinsonism patients. The most frequent comorbidities for the PD patients were cerebrovascular disease (42.53%), hypertension (33.17%), diabetes (10.60%), chronic pulmonary disease (6.98%), and paralysis (5.53%). For the parkinsonism patients, cerebrovascular disease (53.22%), hypertension (39.00%), diabetes (11.66%), paralysis (11.06%), and dementia (7.05%) were more common. Parkinsonism patients more frequently had cerebrovascular disease, dementia, paralysis, hypertension, weight loss, and drug abuse than patients with PD, but they had a lower prevalence of solid tumor without metastasis and mild liver disease [8, 9].

Dementia occurs as part of the neurodegenerative process, which directly leads to a decrease in the quality of life of PD and parkinsonism patients. A systematic review showed that the prevalence of dementia in patients with PD (PDD) ranges from 17.4 to 31.5%, with an average of 24.5%, which is higher than that in our cohort. The prevalence of dementia in our Colombian cohort is 4.9% for all patients and 6.9% for patients aged 65 years and older, which is considerably higher than the prevalence of 5.14% observed in the general Chinese population aged 65 years and older [4, 10].

In addition, a recent meta-analysis shows that the pooled prevalence of mild cognitive impairment associated with PD was 40% more frequent for multiple domain subtype. Currently, it is considered that mild cognitive impairment is a risk factor for the development of dementia [11, 12]. The prevalence of mild cognitive impairment (PD-MCI) in patients with PD is in a range of 20–50%, and these patients are at high risk of developing dementia [13]. In a recent review on cognitive impairment in

patients with PD, it was reported that in the long term the progression of the disease can generate dementia in more than 75% of patients, which is closely linked to the disease duration of 10 years or more [14]. Finally, PDD and PC-MCI have a great impact on quality of life in patients, and their caregivers [15]. Thus, it is necessary to understand deeply and broadly the motor and non-motor spectrum of the disease in order to find novel therapeutics and preventive approaches.

3. Pathophysiology

The clinical and pathological changes associated with PPD are complex. The following section summarizes the genetic and histological changes associated with the pathophysiology of dementia in these patients.

3.1 Genetics of PD dementia

Although the genetic risk factors for PD have been investigated, much less is known about the genetic factors associated with the development of dementia in PD. According to some studies, the prevalence of PDD is lower in patients with genetic PD. However, this will depend on the gene variant and other comorbidities that predispose the development of cognitive disorders. Some of the most important genes are discussed below:

- **PARK1:** patients with duplication or triplication of alpha-synuclein gene (α -Syn) have more severe motor progression and worse cognitive prognosis [16] compared to those without the mutation. Although the evidence suggests that the higher the number of replications, the lower the age of onset of cognitive impairment. Of all genes, this seems to be the most related to dementia. More studies are needed to confirm these findings [17].
- **PARK2:** according to some case series, mutations in PARK2 do not seem to cause cognitive decline [18].
- **PARK14:** PLA2G6 mutation could show heterogeneous phenotype including dementia.
- **DJ-1:** due to its low prevalence, there is no clear relationship between DJ-1 and a particular PD cognitive phenotype. There are some reports of dementia within the clinical spectrum of DJ-1 mutations. In a large population-based survey, there was no evidence for an increased risk of dementia in carriers of DJ-1 deletion [19].
- **LRRK-2:** there is conflicting evidence between this mutation and the development of dementia. In a large Algerian cohort of 106 patients (34 mutated), there was no relationship between the presence of mutations and cognitive abnormalities [20, 21].
- **PINK1:** due to its low prevalence, there is conflictive evidence on the relation between PINK1 and PD dementia or cognitive decline [22].
- **APOE4:** the presence of A β plaques and neurofibrillary tau tangles (NFT) are characteristic of cognitive impairment in AD. But, in PD patients, therefore, the APOE ϵ 4 genotype is an additional risk factor to converse to PDD.

Although, some large cohort studies suggest there is no increased risk for developing dementia in carriers [23].

- GBA (glucocerebrosidase): this gene encodes a lysosomal membrane protein that cleaves the beta-glycosidic linkage of glycosylceramide, an intermediate in glycolipid metabolism [24]. Some studies suggest worse cognitive performance in patients with mutations in this gene. Even in some cohorts, it has been considered an independent risk factor for the development of dementia. Mutations in glucocerebrosidase are a major genetic risk factor for PD and increase susceptibility to dementia in a Flanders-Belgian cohort [25].

3.2 Histological changes in patients with PD dementia

Genetic and environmental factors lead to protein misfolding, aggregation, and finally, the neural loss that is reflected in histological changes as mentioned below.

The pathologic findings for PDD include Lewy bodies (LBs), AD pathology, and cerebrovascular disease, among others. Apparently, the inclusions type and the brain localization influence the severity and type of cognitive impairment. LBs and Lewy related pathology (LRP: Lewy neurites) localized in neocortex and limbic areas are related to the risk of suffering dementia with a rapid progression and lower scores in all cognitive domains [26]. On the other hand, limbic distribution is associated with visuospatial skills impairment [27]. LB densities in the temporal lobe were significantly higher in cases with PDD, compared to PD without dementia [28]. Furthermore, concomitant aggregation of b-amyloid (AD pathology) with LRP is associated with PDD. There is evidence in cell models that α -synuclein contributes to deposition of tau and b-amyloid, leading to a summative effect over the risk of PDD [29, 30].

The association of PDD and small vessel disease and cerebral amyloid angiopathy remains elusive because these are also common findings in brains of elderly people [26].

4. Biomarkers of Parkinson's disease dementia

Recent research is focused on the study of molecules or biomarkers related to the pathophysiological mechanisms of PD that can contribute in clinical practice to the diagnosis, prognosis, and monitoring of the progression of neurological diseases.

The most promising results have been obtained from neurofilament light chain protein (NFL), α -synuclein species, lysosomal enzyme activities, and classic AD biomarkers such as amyloid beta peptide 1–42 ($A\beta_{42}$) and tau protein. An important innovation for diagnostic is the identification of forms of α -synuclein prone to aggregation in early stages of PD [31]. Furthermore, the highest diagnostic accuracies to identify PD patients have been obtained from the combination of different biomarkers (**Figure 1**) [32]. However, these studies require further validation for clinical practice [33–35].

4.1 Cerebrospinal fluid and serum

Prediction of cognitive decline and progression to dementia in PD patients could be a promising tool in clinical practice. Some biomarkers used for AD in cerebrospinal fluid (CSF) have shown that low concentrations of $A\beta_{42}$ in CSF are associated with worse cognitive scores and could predict cognitive impairment in patients with PD [36, 37].

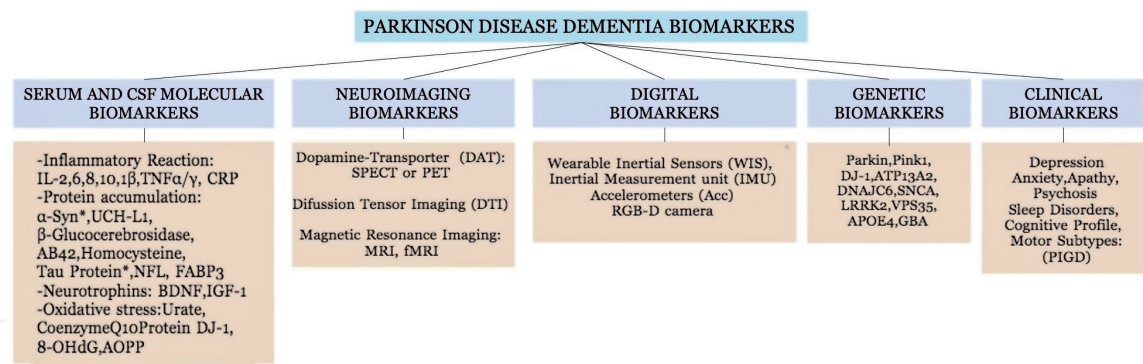


Figure 1.
Main biomarkers of PD. Figure 1 summarizes the serum, imaging, digital evaluation, and genetic and clinical biomarkers associated with the pathophysiology and course of dementia in Parkinson's disease. TNF: tumor necrosis factor; CRP: C reactive protein; α -Syn: α -synuclein; UCH-L1: ubiquitin C-terminal hydrolase-L1; AB42: amyloid β peptide 1–42; NFL: neurofilament light chain; FABP3: heart-like fatty acid binding protein; BDNF: brain-derived neurotrophic factor; IGF-1: insulin-like growth factor-1; AOPP: advanced oxidation protein products; 8-OHdG: 8-hydroxy-2'-deoxyguanosine; MRI: magnetic resonance imaging; DAT: dopamine transporter; TCS: transcranial sonography; PET: positron emission tomography; SPECT: single photon emission computed tomography; WIS: wearable inertial sensors; and IMU: inertial measurement unit. *Includes species.

The performance and prognostic value of CSF A β 42 improved when combined with other biomarkers of CSF. CSF A β 42 levels <626 ng/L was associated with a hazard ratio (HR) of 2.8 (95% CI 1.4 to 5.8) for the development of dementia within 5–9 years of follow-up. When the ratio of CSF NFL, FABP3, and A β 42 is more than 2.1, the HR values increased to 11.8 (95% CI 3.3–42.1) [38]. In addition, if the clinical characteristics are analyzed with CSF A β 42 levels, its prognostic value is further improved [39]. Thus, it has also been determined that low A β 42 values could predict early psychosis in PD patients within 3–4 years of follow-up [40].

Both, total α -synuclein and homocysteine (Hcy) in CSF have shown contradictory results as a predictor of cognitive impairment [31, 32, 41, 42]. Some neuroinflammatory reaction molecules such as interleukin 8 (IL-8) and C-reactive protein (CRP) levels in CSF are related to decreased MOCA scores in PD patients and PDD patients, respectively [43–45].

It has recently been determined that the blood neurofilament (NFL) can discriminate between (PD) and atypical parkinsonian disorders (APD) with the same precision as in CSF, which would facilitate its use in the differential diagnosis of parkinsonian disorders, and would also allow to correlate the severity and progression of the motor and cognitive functions of PD [46].

Progression in motor disability in PD patients was associated with α -synuclein species concentrations [31]. Both the combination of ratio of phosphorylated tau to A β 42 and CSF total tau have been found to have a correlation with a faster decline of performance in total unified Parkinson's disease rating scale (MDS-UPDRS) over time. Tau pathology, as assessed by CSF phosphorylated tau, seems to have a role in accelerating motor progression [47]. Some studies suggested that there is a positive correlation between DJ-1, advanced oxidation protein products (AOPP), and 8-OHdG levels, and a greater severity of the disease [32, 42, 48–50].

4.2 Neuroimaging

Advances in neuroimaging allow the identification of non-invasive biomarkers to confirm the diagnosis and possibly know the severity of the disease and also determine the functional prognosis. The Braak progression model does not respond precisely to the behavior of the clinical profiles or to the progression of parkinsonism in a real scenario, where epigenetic variables will be related to the evidence of

overlapping between different protein aggregations and alterations of the midbrain-striatal-cortical loop.

Dopamine transporter single photon emission tomography (DAT-SPECT) provides a semi-quantitative assessment of striatal dopaminergic deafferentation. This PD biomarker has a strong correlation between the amount of dopamine transporters in the striatum and the number of dopaminergic neurons in substantia nigra [51, 52].

The combined analysis of various imaging techniques will allow characterizing the baseline alterations related to the disease using DAT-SPECT, DTI, and MRI [53–55]. Functional MRI (fMRI) can show variation of connectivity functional network by detecting oxygenated hemoglobin and deoxyhemoglobin content in brain regions in PD patients [7, 56]. These changes can be present before motor symptoms, and can detect PD patients from normal individuals with a sensitivity of 100% and a specificity of 89.5% [57, 58].

The combined blood and imaging biomarkers such as MR planimetric measurements and NFL serum levels, provided accurate differentiation of PD versus multiple system atrophy (MSA) and progressive supranuclear palsy (PSP) patients. The combined overall diagnostic yield was an accuracy of 83.7% (95% CI 69.8–90.8%) [59].

4.3 Digital data

Ecological and objective measurements made with wearable technology in patients' homes are a reality. The analysis of gait domains in PD patients and its changes over time is a promising biomarker to track normal aging and the progression of the disease as the response to treatment [60].

Considering the functional interdependence of cognition and gait, objective analysis of gait and changes in certain gait domains may be a sensitive marker of the risk of cognitive impairment in patients with PD, observing greater asymmetry and variability in stride time, swing time, and posture compared to AD and Lewy body dementia (LBD) [61].

New technologies applied to the objective measurement of neurological symptoms or diseases will have to be subjected to an adequate scientific validation process.

5. Clinical approach: the continuum of cognitive impairment and dementia in PD

It has been reported that PD patients may have normal cognition at the onset of the disease, although some patients present PD-MCI in the early stage of the disease and it is more frequent with the increment of years of the disease and older age [62]. In 2019, the International Parkinson and Movement Disorders Society (MDS) concluded that the diagnosis of level I PD-MCI is a risk factor to PDD while taking into account variables like age, sex, education, PD motor sign severity, and depression [63].

The most frequent alterations suggest that there are heterogeneous profiles that can be amnesic and non-amnesic. In general, it has been described that the most frequent deficits involve executive dysfunction, decreased attention, and visuo-spatial dysfunction, as well as in global cognition. However, it is recognized that the PDD extends beyond dysexecutive syndrome to include deficits in recognition memory [64] and visual perception, as well as visual hallucinations and cognitive fluctuations [65]. These findings would indicate that cognitive problems could occur in patients in prodromal stages, which would be in line with the evidence

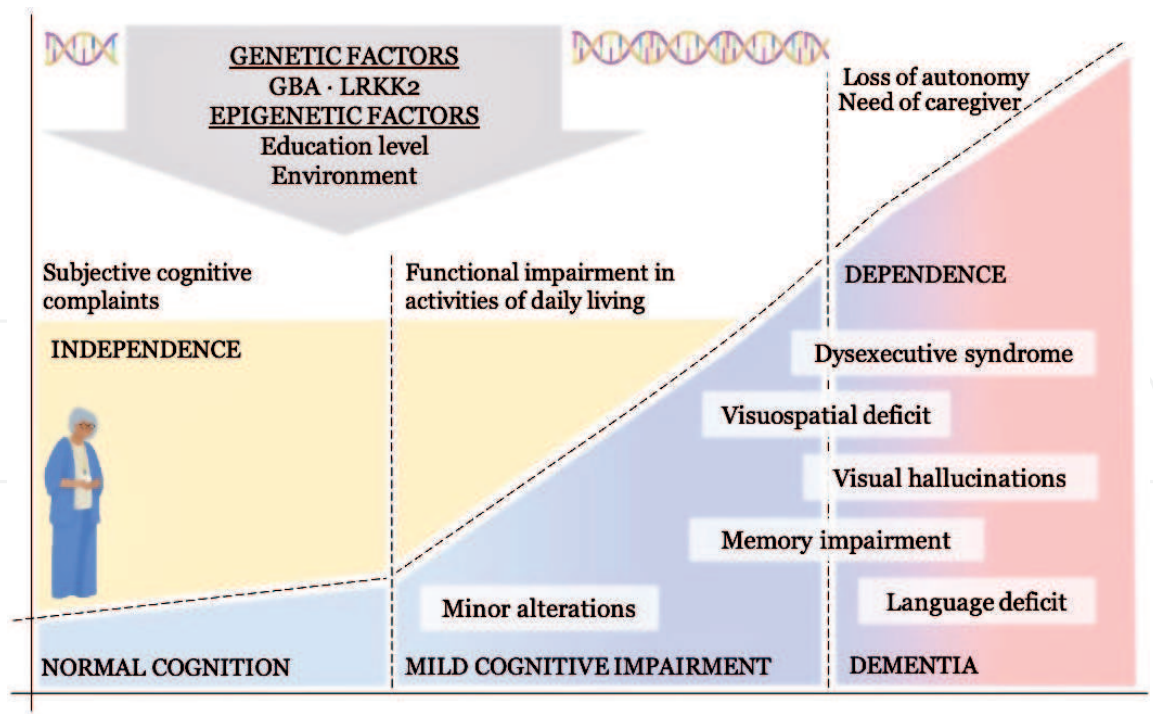


Figure 2.
The continuum of cognitive impairment in PD patients. Figure 2 shows the relationship between genetic and epigenetic factors in the natural course of cognitive decline in Parkinson's disease.

in favor of newly diagnosed or early stage patients already exhibiting deficits in cognition (**Figure 2**) [66].

The main cognitive domains that underlie the presence of PDD have been widely described, however, the compartmentalization is given to understand the complexity of clinical heterogeneity since neural networks interact and they overlap each other to finally define a cognitive function that is influenced by distributed individual actions [67]. Likewise, the existence of a “dual hypothesis” regarding the cognitive component has suggested that the PD-MCI could be a dopamine-dependent profile closely related to the executive and working memory deficit, while the PDD could be a superordinal stage that it would imply the presence of other neurotransmission systems, which generate a picture of rapid progression exhibiting deficits in learned movements (apraxia), in recognition (agnosia), and in language (aphasia) in these patients [68].

Executive impairments in PD are due to the damage of connections between dorsolateral and ventrolateral frontal cortices with the globus pallidus internus and head of the caudate, as well as degeneration of mesocortical pathways with hypometabolism and atrophy prefrontal, insular, and cingulate cortices. Attention problems detected in the early stage of PD and PDD are related to frontal-parietal networks. Memory complaints are common even at the early stage of PD, although subjective memory complaints (SMC) at that point are more related with attentional deficits. However, with the progression of PD-MCI to PDD dementia, memory impairments are similar to those found in AD, in relation to the difficulties with recalling and recognition, which are associated in PDD patients with medial temporal lobe atrophy. Further neuropsychological research is needed to make a proper association on this [67].

Visuospatial and visuoceptive alterations are prominent of PDD, explained by deterioration in occipito-parietal connections (dorsal and ventral pathway related with spatial location and object recognition, respectively). Visual hallucinations are a hallmark of PDD, and a relevant symptom which suggests the interrelationship with LBD. Different networks are implicated in the visual hallucinations

such as middle occipital, inferior parietal lobule, nucleus basalis Meynert (NBM), and dysfunctional sleep-wake cycling with REM (rapid eye movement) sleep behavioral disorder (RBD) [67, 69].

Since it is well established, dopamine loss is the key of motor features, and the cornerstone of the PD treatment. However, acetylcholine, noradrenalin, and serotonin are responsible for the presence of non-motor symptoms, especially cognitive impairment. Loss of cholinergic neurons in NBM is found in 54–70% of PDD patients as well as 40% loss of neurons in brainstem cholinergic nucleus and the pedunculopontine nucleus [70]. The cholinergic diffused afference to cerebral cortex disrupts focused attention, memory encoding, and visual discrimination, and it is implicated in the generation of visual hallucinations [67, 69, 71].

Furthermore, noradrenalin deficit from locus coeruleus involving outputs to the thalamus, amygdala, and cortex contributes to damage in executive control, attention, and maintenance of arousal [71]. The role of the serotonin system has been less investigated in PDD than the neurotransmitters exposed above. It is known there is a reduction in the serotonergic transmission to caudate nucleus [69].

Neuroimaging studies have reported that frontal-subcortical and cortical circuits could be involved in the development of PDD. The heterogeneous profile exhibits a decrease in dopaminergic frontal-striatal networks as well as a wide decrease in cholinergic cortical networks and a degeneration in the limbic-paralimbic system [72]. On the other hand, studies that combine cognitive measures with neurophysiological markers have demonstrated that posterior and frontal-executive cognitive task performance were associated with high risk of conversion to PDD [73].

The identification of PD-MCI is a critical point to management and potential clinical trials of pharmacological therapies. Moreover, the correct diagnosis of PD-MCI and PDD depends of the use of recommended cognitive tests for PD patients [74]. PD-MCI criteria include level I based on a screening evaluation to global cognition and level II based on comprehensive neuropsychological assessment [75]. The MDS Task Force recommends three global screening scales for use when it is not possible to do a comprehensive neuropsychological testing; the scales are the following: Montreal Cognitive Assessment (MoCA), Mattis Dementia Rating Scale, and Parkinson's Disease-Cognitive Rating Scale (PD-CRS) [76].

Because cognitive impairment in PD is beyond cognition, it is useful to ask to the patient and caregiver about subjective complaints, behavioral changes, and quality of life (**Table 1**). In addition, for the diagnosis of PDD, it is important to evaluate the functional independence in activity daily life (ADL) with questionnaires or scales recommended: Parkinson Disease Cognitive Functional Rating Scale (PD-CFRS), Functional assessment questionnaire, and the pill questionnaire [77].

Table 1 summarizes the affected neural networks and their effect on the patient's cognitive domains with the neuropsychological tests recommended for their evaluation.

5.1 The cognitive impairment, non-motor symptoms, and motor subtypes

Interplay between motor and non-motor symptoms has been described with the objective to explore the relationship with different neurotransmitters systems related in the disease progression. Depression, anxiety, apathy, psychosis, fatigue, and sleep problems are common in PDD or even PD-MCI [78].

Also, the different clinical phenotypes of PD can relate the motor symptoms (MS) to non-motor symptoms (NMS). Factors that could contribute to the progression of the disease are also related to advanced age, the severity of motor symptoms, as well as the postural instability gait disorder (PIGD) subtype, the presence of

Neural networks	Cognitive domains	Neuropsychological tests
Nigrostriatal dopamine network	Executive function Decision making/ reversal learning	<ul style="list-style-type: none">• Wisconsin card sorting test (WCST)
Mesocortical dopamine network	Executive function Inhibitory control	<ul style="list-style-type: none">• Stroop test; frontal assessment battery (FAB)
	Working memory	<ul style="list-style-type: none">• Phonological verbal fluency• Trail making test part B (TMT-B)• WAIS-IV digit span
Noradrenergic network	Orientation	<ul style="list-style-type: none">• WMS-IV orientation
	Executive attention	<ul style="list-style-type: none">• Trail making test part A (TMT-A)
Cholinergic network	Visuoperceptual deficits	<ul style="list-style-type: none">• Judgment of line orientation (JLO)Visual object and space perception (VOSP) batteryWAIS-IV block design
	Memory deficits	<ul style="list-style-type: none">• Hopkins verbal learning test (HVLTL); Rey auditory verbal learning test (RAVLT)Wechsler memory scale (WMS-IV): logical memory, designs and visual reproduction TesttRey-Osterrieth complex figure test (RCFT)
Mesial-frontal network Orbitofrontal cortex network Basal ganglia and dorsolateral prefrontal cortex network	Psychological status	<ul style="list-style-type: none">• Beck depression inventory (BDI-II)
	Behavioral disturbance	<ul style="list-style-type: none">• Beck anxiety inventory (BAI-II)
		<ul style="list-style-type: none">• Frontal systems behavioral rating Scale (FrSB)
		<ul style="list-style-type: none">• Neuropsychiatric inventory questionnaire (NPI-Q)
	Quality of life	<ul style="list-style-type: none">• Parkinson disease questionnaire-39 (PDQ-39)

Table 1.
Neural networks affected in PDD.

visual hallucinations, and associated cognitive deficits to the cortical-posterior profile. Some NMS such as depression and anxiety have been related to specific motor subtypes, and it has been reported that poorer NMS profile are associated with PIGD subtype [79], besides history of falls and motor complications as an effect of pharmacological therapy [80].

Furthermore, PDD is more frequent among PIGD subtypes, and balance and gait disorders predict other non-motor symptoms (NMS) like hallucinations, urinary problems, and daytime sleepiness (12); whereas the alterations of attention and executive domain, which are related to frontostriatal deficits, could be considered a more stable profile [68]. Moreover, other studies have found that progression to PDD would also be associated with poor performance in executive tasks such as verbal fluency as well as other tests associated with cognitive flexibility, inhibition, and concept formation (commonly evaluated using the trail making test (TMT) part B, Wisconsin Card Sorting Test (WCST), and Stroop test) [81, 82].

The importance of detecting individual variables, as well as biomarkers for the heterogeneity of progression to PDD, then becomes useful information to contribute to the clarification of the pathophysiological mechanisms of cognitive impairment in patients with PD [83].

In PD patients, the loss of dopaminergic neurons in the substantia nigra impacts the connections with the prefrontal cortex, which has suggested that it may attenuate the cognitive component in these patients, as well as compromise the ability to cognitively compensate for the deficit in gait. Additionally, acetylcholine is related with attentional processes of the prefrontal cortex and has been strongly associated with a decrease in gait speed. In some patients with PD, this relationship may be exacerbated by freezing gait episodes, since it has been reported that this subgroup of patients has a worse performance in visuospatial skills tasks compared to those who have not, which could be related to a decrease in gray matter in posterior cortical areas [84].

In studies carried out with different motor subtypes and patients with PD-MCI, it has been suggested that scores in the visuospatial domain are correlated with the stability factor, while the executive domain does not correlate with any factor, probably suggesting a more general role of executive functions. The processing of visual information is important during the planning and the control of locomotion in patients with PD. Additionally, low scores in stability factor was inversely associated with advanced stages on the Hoehn and Yahr scale, worse scores in MDS-UPDRS part III, suggesting that there is a specific relationship between motor progression, instability, and visuospatial alteration [85].

The relationship between the different aspects of balance and gait with the cognitive domains suggests that they are mediated by multiple neural pathways. Degeneration in the dopaminergic systems could contribute to cognitive deficits and the PIGD subtype, while degeneration within the cholinergic system has been proposed as a factor that contributes to cognitive and axial symptoms in PD patients. Hypofunction of the cholinergic system has been implicated in impaired executive functioning as well as a greater slowdown in gait speed in patients with PD [86].

6. Treatment

So far, there are no available treatments to cure or stop the progression of the synucleinopathies; hence, offering the best balance in the control of motor and non-motor symptoms of the PD must be a main clinical objective. Due to the multisystemic and progressive nature of neurodegeneration, it is necessary to periodically update the inventory of cognitive, behavioral, and affective symptoms, alongside the motor and general health status, and also to determine the functional impact in daily life activities as well as on the social and working environment [87–89].

It is important to identify and strengthen the support network of caregivers to diagnose and give an appropriate support to the symptomatic complexity of each patient by a multidisciplinary team, which aims to improve their quality of life, reduce disability and health care costs, as well all risks mainly related to cognition and social behavior.

The adequate identification of high-risk clusters would allow the development of subtype specific therapeutic objectives. Moreover, recognizing the non-motor symptoms of high impact of quality of life such as mood disorders, sleep or eating disorders, and behavioral and social behaviors disorders could allow to define an appropriate clinical care [90].

Behind a specific symptom, there are brain areas or hypoactive or overactive functional associative networks with altered neurotransmitter systems such as dopaminergic, cholinergic, serotonergic, glutamatergic, or noradrenergic [26, 65]. For this reason, the analysis and functional neuroanatomical correlation on the temporal course of the disease as well as the cognitive profile is necessary for the

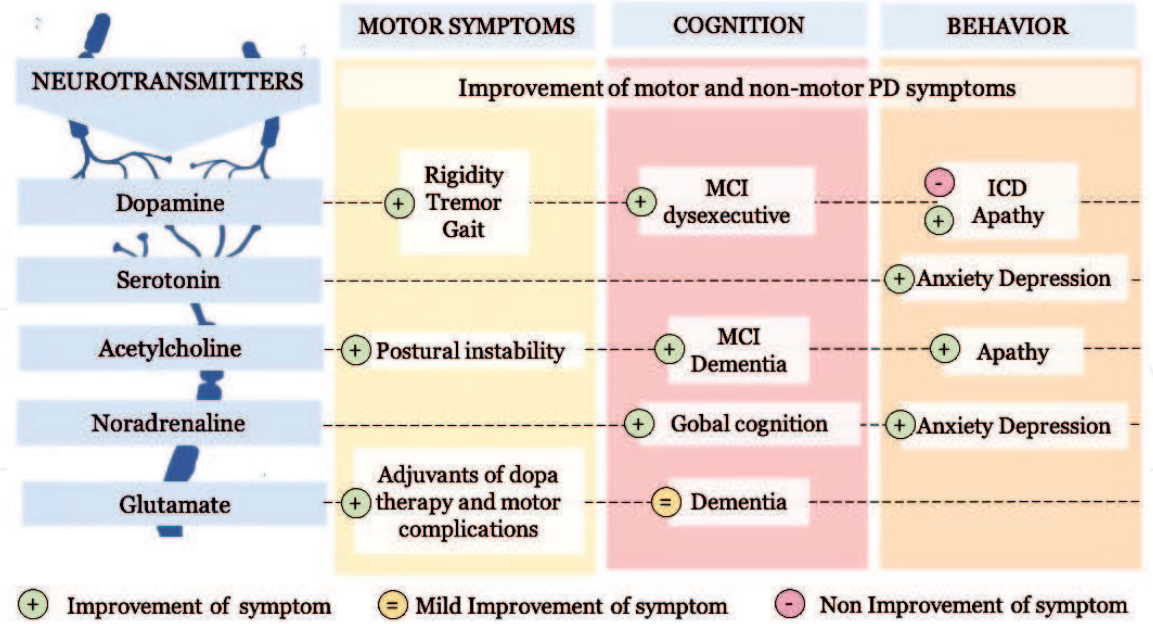


Figure 3. Neurotransmitters systems related with motor and non-motor symptoms in PD. Figure 3 shows the interaction between neurotransmitters and PD symptoms with the estimated response in each category based on clinical experience.

therapeutic selection and to reestablish, as far as possible or partially, the neurochemical and functional balance (Figure 3).

Dopaminergic stimulation can cause some cognitive benefits on frontal executive functions, however, when the patient has motor complications, it could facilitate the appearance of some affective and cognitive fluctuations and could exert a negative effect on cognition [91].

Cholinergic denervation through different mechanisms affects cognition in patients with PD. For that reason, from cholinesterase inhibitors, Rivastigmine is the one with the best evidence of clinical efficacy and safety by improving some cognitive and neuropsychiatric domains. Such evidence is not similar for mild cognitive impairment, which is common in the disease [87, 92]. A possible application of the cholinesterase inhibitors is to improve some gait domains and reduce the risk of fall, by increasing the cholinergic stimuli in the brain areas related to motor and cognitive control of gait [93].

Despite finding a glutamatergic hyperactivity that causes the progression of cognitive deficit in PD, memantine, an N-methyl-D-aspartate (NMDA) antagonist has shown a weak efficacy in improving cognitive functions [94].

The use of atomoxetine, a selective norepinephrine reuptake inhibitor (SNRI), was not effective for the treatment of depressive symptoms in PD, but was associated with improvement in global cognitive performance and daytime sleepiness; however, there is insufficient evidence on new indications for this drug [95].

Likewise, the use of transcranial direct-current stimulation (t-DCS) as well as repetitive transcranial magnetic stimulation (r-TMS) to improve the cognitive impairment has not reached enough evidence and recommendation in order to be recommended [96].

Both the interactions and the potential side effects can aggravate the cognitive state and also produce psychosis, starting with the medicines used in the control of motor symptoms such as anticholinergics trihexyphenidyl, biperiden or benztropine, dopamine antagonist, and amantadine. It is important to monitor daily the interactions of medicines used in treatment of symptoms or concomitant chronic diseases and the potential interactions with the indicated medicines for

the control of neurological symptoms. Especially with benzodiazepines, anticholinergics/antimuscarinics used in gastrointestinal or bladder disorders, tricyclic antidepressants, or antipsychotic drugs, several observational studies have shown an association between exposure to anticholinergic drugs and the risk of cognitive impairment [97].

Rehabilitation as well as cognitive stimulation, whose objective is to develop strategies to improve or maintain functionality in daily activities, must be customized according to the phenotype or the cognitive profile in each patient's context [98, 99].

7. Conclusion

PDD is a rising, broad, and complex spectrum disorder with a high burden to patients and their caregivers. The prompt recognition of PD patients with red flags to progress to PDD is crucial to early enrollment in a multidisciplinary and therapeutic approach to diminish disease load. Nowadays, therapeutic options are limited. However, the advent of molecular, cellular, and technological advances creates a promissory future to specific treatment, allowing truly improvement in the patient's and caregiver's quality of life.

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