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Current level of knowledge about Parkinson's disease cognitive impairment

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Abstract

Background: Parkinson's disease (PD) affects more than 1% of the population aged over 65 years and manifests with both motor symptoms – bradykinesia, rest tremor, rigidity, and non-motor symptoms. Cognitive impairment and dementia are recognized non-motor symptoms that can significantly affect the quality of life of both the patient and caregivers and are a risk factor for institutionalization in nursing homes and a risk factor for early mortality. Cognitive impairment is frequent in Parkinson's disease (PD) that can develop even before the diagnosis of Parkinson's disease based on its motor features.
Conclusions: There are several clinical, molecular, and imaging factors that constitute risk factors for the development of Parkinson's disease dementia, in which basal cholinergic and prefrontal dopaminergic systems are involved. Histological changes are Lewy-body, Alzheimer, but also vascular pathology. Clinically can be distinguished subjective cognitive decline, mild cognitive impairment and, subsequently, Parkinson's disease dementia. There are no remedies with a proven effect to prevent the occurrence of cognitive decline in PD. The only approved drug for already developed D-PD is the cholinesterase inhibitor – donepezil. Non-pharmacological interventions are thought to be beneficial. A multidisciplinary approach to cognitive impairment is recommended, with specific pharmaceutical treatment of the cognitive disorder and comorbidities, and appropriate rehabilitation.
Key words: Parkinson's disease, mild cognitive impairment, dementia.

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Introduction

Parkinson's disease (PD) affects more than 1% of the population aged over 65 years [1] and manifests with both motor symptoms – bradykinesia, rest tremor, rigidity, and non-motor symptoms [2]. Cognitive impairment and dementia are recognized non-motor symptoms that can significantly affect the quality of life of both the patient and caregivers and are a risk factor for institutionalization in nursing homes and a risk factor for early mortality [3]. Cognitive impairment can develop and manifest at any stage of the disease, even before the diagnosis of Parkinson's disease based on defining motor symptoms and most often begins insidiously [4]. There are several clinical, molecular, and imaging factors that constitute risk factors for the development of Parkinson's disease dementia (D-PD). Executive and visuospatial impairments, visual hallucinations, changes in cerebrospinal fluid and/or blood serum biomarkers, and structural and functional imaging changes are recognized as risk factors of D-PD [5]. In D-PD, the basal cholinergic and prefrontal dopaminergic systems are involved; and histological changes of Lewy-body type, Alzheimer type, but also vascular type are observed [6]. Subjective cognitive symptoms, which can appear even from the premotor and early stages of PD, progress to mild cognitive impairment and, subsequently, to Parkinson's disease dementia. There are no remedies with a proven effect to prevent the occurrence of cognitive disorders in PD or to treat the minor cognitive deficit associated with PD, while the only approved drug for already developed D-PD is the cholinesterase inhibitor – donepezil [7]. Physical training and cognitive training are thought to be beneficial. A multidisciplinary approach to cognitive impairment is recommended, through the administration of specific pharmaceutical treatment of the cognitive disorder, treatment of comorbidities, and appropriate rehabilitation.

Epidemiology of cognitive disorders in Parkinson's disease. Epidemiologic studies of PD do not always include minor cognitive impairment associated with Parkinson's disease (MCI-PD) or dementia associated with Parkinson's disease (D-PD). Therefore, data on the epidemiology of cognitive impairment in PD are incomplete. About 30% of newly diagnosed patients with PD presented subjective complaints related to memory; their risk was significant for developing MCI within the next 2 years compared to patients who had no memory-related complaints [8]. Up to 25.8 – 64% of patients with PD suffer from MCI-PD [9]. At the time of diagnosis of PD, MCI is found in approximately 20% of patients [10]. A multicenter prospective longitudinal study of PD patients found that at the time of PD diagnosis, 20.2% had MCI, and at 5 years of follow-up, its

incidence increased to 40–50% [11]. Two cross-sectional studies estimated the prevalence of MCI-PD to be 33% and 64%, respectively [12]. At the same time, the prevalence of MCI in the general elderly population (60 - 90 years) is much lower and varies between 16 and 20% [13]. The conversion rate to D-PD is significant in PD patients with MCI and is almost 60% at 5 years of follow-up [11]. More than 75% of patients, who develop cognitive decline in the early stages of PD, will later develop Parkinson's disease dementia, but a stabilization of cognitive function or even a reversal from MCI-PD to normal cognition has also been reported in approximately 25% of MCI-PD patients [11]. The results of longitudinal studies show that the risk of patients with PD to develop dementia is up to 6 times higher than that of the age-matched healthy population [14]. In the population older than 60 years, the prevalence of dementia is 5-7% [15]. 3 - 4% of dementia is thought to be caused by PD, and the estimated prevalence of D-PD in the general population aged over 65 is 0.2 to 0.5% [16]. Research indicates an association between the prevalence of D-PD and the duration of PD: the cumulative prevalence of D-PD 5 years after diagnosis is 17%, 10 years after diagnosis – 46%, and 20 years after diagnosis – 83% [17]. After 10 years of PD evolution, dementia is present in approximately half of the patients, and after 20 years – in most patients [5]. Several general and clinical characteristics are associated with an increased risk of developing cognitive decline. Some predictors, which were independently associated with the development of cognitive impairment and/or dementia, have been described: (1) general factors: older age, male gender, lower education level, older age at onset of PD, (2) non-motor symptoms: visual hallucinations, depression/mental state, hyposmia/anosmia, orthostatic hypotension, (3) motor signs: akinetic phenotype, postural instability, (4) disease severity: high motor impairment score, high bradykinesia score, advanced Hoehn and Yahr stage, (5) response to treatment: cognitive adverse effects of dopaminergic treatment, poor therapeutic response to dopamine agonists, (6) specific cognitive deficits: posterior cortical cognitive deficits, frontal executive dysfunction, (7) comorbidities: cerebrovascular disease, diabetes, obesity, heart disease, (8) lifestyle factors: alcohol consumption, smoking [2, 18, 19].

Pathophysiology of cognitive decline in Parkinson's disease. PD patients suffer an early cholinergic degeneration in the anterior basal part of the brain, but abnormalities of the prefrontal dopaminergic system, and other neurotransmitter systems (noradrenergic and serotonergic) of the neocortical, limbic and basal ganglia regions are also characteristic [20]. Along with the early loss of dopaminergic neurons in the substantia nigra, an abnormal deposition of α-synuclein in the Lewy bodies also occurs; first – in the cholinergic and monoaminergic neurons of the brainstem and olfactory system, which leads to significant synaptic deficiencies [21].

Compared to patients with PD and normal cognition, those with MCI-PD and D-PD, show an increased dopaminergic loss in the region of the frontal, parietal and temporal cortex [5]. Dopamine depletion in the nigrostriatal pathways has been involved in the impairment of working memory, planning/sequencing, task switching, response inhibition, recall, verbal fluency, and psychomotor speed [22]. On the other hand, impairments in amnestic memory, language, and visuospatial impairments involve neurotransmitter systems, such as acetylcholine, noradrenaline and serotonin [23].

Several studies have identified associations between the progressive loss of cerebral noradrenaline and cognitive decline in patients with PD [24]. Dopaminergic, noradrenergic, and serotonergic CSF markers were compared in healthy controls, PD patients and D-PD patients. Progressive changes were found in all markers, but only the noradrenergic markers were significantly reduced in all D-PD patients and in all brain regions [25].

Loss of cortical cholinergic innervation is independently associated with the cognitive decline of PD, and its association with a greater dopaminergic denervation in the caudate nucleus correlates with an even more pronounced cognitive decline [26]. The density reduction of cholinergic neurons in the anterior basal cortex and of their projections to the neocortex, amygdala and hippocampus is associated with cognitive decline in patients with de novo PD, and is predictive of cognitive decline in patients with PD and normal cognition [5, 27]. The loss of cholinergic projections from the forebrain to the hippocampus correlates with memory deficits and conversion to D-PD [27]. The loss of brainstem serotonin is associated with non-motor symptoms of PD (depression, anxiety) and correlates with β-amyloid deposition [28]. The loss of cholinergic fibers is more pronounced than the loss of cholinergic neurons in patients with D-PD [29]. In MCI-PD there is a loss of cholinergic fibers and a decrease of cholinergic activity in the hippocampus, while in D-PD a progressive deposition of α-synuclein occurs, with subsequent dysfunction, not only in the hippocampus, but also in the basal forebrain [30].

Morpho-pathological changes in PD-associated cognitive dysfunction include Lewy bodies and neurites, coexisting Alzheimer's tau and amyloid pathology, and ischemic microvascular changes [31]**.** The most common neuropathology in D-PD is limbic and/or neocortical Lewy pathology [32], but other types may coexist. Alzheimer-type and Lewy-type pathologies frequently coexist, and this coexistence is a better predictor for the development of D-PD than the severity of either pathology alone. Neuropathological studies argue for the dual hypothesis of cognitive impairment in PD. A morpho-pathological study showed that 38% of D-PD patients only had Lewy body accumulations, 59% had Lewy bodies in combination with beta-amyloid plaques, and 3% had Lewy bodies, beta-amyloid plaques, and neurofibrillary tangles [33].

An increased share of white matter hyperintensities has been reported in subjects with PD who later progressed

to dementia [34]. The total volume of white matter hyperintensities in patients with early PD and in patients with MCI-PD, was predictive for the occurrence of longitudinal cognitive decline [35]. A prospective study found that progression to dementia was more frequent in PD patients who had a moderate-severe ratio of parieto-occipital white matter hyperintensities associated with low CSF β-amyloid levels [36]. At the same time, other studies found no correlation between the severity of subcortical small vessels injury and dementia [37].

Certain genetic polymorphisms are associated with the onset and development of PD-related cognitive dysfunction. In patients with Parkinson's disease and GBA mutations, diffuse neocortical pathology with Lewy bodies is more common and is associated with hallucinations, cognitive decline, or early dementia [38]. Executive functions, visuospatial skills and working memory are affected. COMT Val/Val polymorphisms stimulate dopamine catabolism and lead to a decrease in postsynaptic dopaminergic stimulation, while Met/Met polymorphisms decrease COMT enzyme activity and lead to increased dopamine levels [39]. Therefore, there is not necessarily an association of the COMT genotype with later cognitive impairment or dementia. COMT genotype is associated with executive dysfunctions based on the frontostriatal system. The MAPT H1/H1 genotype, which influences tau transcription, is thought to be an independent predictor of D-PD and is associated with significant posterior-type cortical cognitive deficits [39].

There are a series of predictive biomarkers of cognitive decline in Parkinson's disease. The function of biomarkers of cognitive decline is to predict the developmental perspective of cognitive decline and dementia in PD [40]. Protein biomarkers are predictive of cognitive decline in Parkinson's disease. Cortical pathological synuclein accumulation in patients with idiopathic PD correlates with cognitive decline, while the lack of Lewy bodies in autosomal recessive PD, caused by Parkin gene mutations, is associated with normal cognitive function throughout the course of the disease [41]. Likewise, in autosomal dominant PD caused by mutations in the LRRK2 gene, in which there are subgroups without Lewy bodies, the risk of cognitive dysfunction is lower, and cognitive impairment and dementia correlate with the presence of Lewy bodies [42]. Autosomal dominant PD due to SNCA [43] and GBA mutations, patients with Gaucher disease and idiopathic PD [44], may frequently manifest cortical Lewy bodies and significant associated cognitive dysfunction. Comorbid morpho-pathological changes, such as cerebrovascular disease and Alzheimer-like changes (hippocampal sclerosis, accumulation of β-amyloid plaques and tau neurofibrillary tangles) may contribute to D-PD [45]. The severity of Alzheimer-type pathology is associated with a shorter time-frame between the onset of motor symptoms and the onset of dementia, as well as a lower survival rate [45] in D-PD and also correlates with the severity of cognitive impairment. Total α-synuclein CSF levels are lower in PD patients compared to controls, with no significant difference between patients with and without dementia [46]. The potentially pathogenic forms of α-synuclein: phosphorylated, ubiquitinated, nitrated, oligomeric, could be more sensitive indicators of underlying disease progression and of a more severe cognitive decline. Thus, oligomeric synuclein has significantly higher CSF levels in patients with D-PD and Lewy body dementia, compared to Alzheimer dementia patients and the control group and correlates with UPDRS-III, MMSE scores, semantic and visuo-perceptual fluency [47]. Plasma levels of total α-synuclein are higher in PD with a more severe cognitive dysfunction and they also correlate with lower Mini Mental State Examination (MMSE) scores [48]. In most studies, the level of CSF ß-amyloid was lower and could predict future cognitive decline in PD patients [49]. This reduced level was associated with worse verbal learning, semantic fluency, and reduced visuo-perceptual scores as well as cortical atrophy in the superior frontal/anterior and precentral cingulate regions— which is predictive for D-PD [50].

Cerebral atrophic changes are predictive structural neurodegenerative biomarkers of cognitive decline. In patients with PD and normal cognition, loss of gray matter volume in the temporal cortex, prefrontal cortex, insula, hippocampus, and caudate nucleus may predict the occurrence of MCI-PD. In MCI-PD, neuronal loss has a pattern of posterior, parietal and frontal cortical involvement, as well as hippocampal atrophy. The severity of this atrophy correlates with the memory decline, and its progression towards the parahippocampal and cingulate gyrus is associated with the progression of cognitive decline in PD. When applied to PD patients, the SPARE-AD Alzheimer's Dementia brain atrophy model predicted long-term cognitive decline in PD patients who were dementia-free at that time point [51].

Functional neurodegenerative biomarkers predictive of cognitive decline. Through PET and SPECT, the activity of acetylcholine and dopamine can be determined. Acetylcholinesterase (AChE; the enzyme which catalyzes acetylcholine breakdown) activity in the lower cortical regions is associated with reduced cognitive performance scores for: attention, memory, and executive function. In D-PD, reduced AChE activity becomes more severe and widespread; it involves the occipital, temporal, frontal, and medial cortex, as well as the thalamus.

Connectivity-biomarkers predictive of cognitive decline in Parkinson's disease. Altered neurotransmitter signaling associated with neurodegeneration leads to dysfunctions of regional brain activity and circuit connectivity in PD. Brain activity, measured by regional glucose metabolism (PET) and regional perfusion (SPECT), is lower in PD patients in the occipital and inferior parietal lobes. Decreased brain activity correlates with performance on neuropsychological tests [52]. PD patients without cognitive decline show a decrease in the functional connectiv-

ity of the right medial temporal lobe and bilateral inferior parietal cortex, in the brain connectivity network; this low connectivity correlates with cognitive parameters. Patients with D-PD reveal decreased connectivity in the inferior occipital gyrus bilaterally, compared to healthy subjects; and in the right frontal gyrus, compared to both non-D-PD patients and controls [53].

A sole biomarker that could represent the multiple pathological substrates of cognitive impairment in PD is not yet available. Therefore, to improve the accuracy of cognitive decline prediction in PD, the following combinations of biomarkers could be used:

(1) patient age + UPSIT score (University of Pennsylvania test) + REM sleep behavior disorder score (RBDSQ) + CSF Aβ42 level + caudate nucleus DAT uptake; this model allows the prediction of cognitive decline in 2 years.

(2) Alzheimer's disease biomarkers: total tau CSF level + phosphorylated tau CSF level + Aβ42 CSF level + APOE genotype + SPARE-AD imaging score; this model separates patients with PD and normal cognition from patients with D-PD with an accuracy of 80%.

(3) PD age at onset + gender + number of years of education + MMSE score at study initiation + presence of depression as a symptom at enrollment + MDS-UPDRS III score at enrollment + presence of GBA gene mutation; this model predicts cognitive impairment with an AUC score of 0.85, and dementia or disabling cognitive impairment with an AUC score of 0.88, within 10 years of disease onset [4, 54].

Clinical characteristics of cognitive decline in Parkinson's disease. Cognitive impairment in PD varies highly in severity, rate of progression, and cognitive domains affected [12]. The phenotypic severity of cognitive impairment ranges from bradyphrenia, subjective cognitive complaints without objective evidence of cognitive dysfunction to MCI-PD later, with a decline that can be highlighted by standardized neuropsychological tests which reflect a worsening of previous functionality, but do not significantly interfere with daily activities; and D-PD with more severe cognitive deficits affecting more than one cognitive domain and significantly interfering with daily activities.

Subjective cognitive decline. Subjective cognitive changes must be monitored; and although they are not always associated with objective changes, in a number of cases, they could herald incipient cognitive decline [8]. In a study of subjective memory complaints in patients with de novo PD (recently diagnosed and/or drug-naive) it was found that about 30% of patients who complained of memory issues had a higher risk to develop MCI-PD during the next 2 years of follow-up compared to patients with no such complaints [8]. Several factors, including affective symptoms, could contribute to progression to MCI-PD [9].

Minor cognitive impairment. The difference between MCI-PD and D-PD is the extent to which cognitive impairment interferes with daily activities. Although cognitive impairment is present in MCI-PD, it does not interfere with daily activities. One or more cognitive domains (attention, executive, language, memory, and visual-spatial functions) may suffer within MCI-PD. Depending on the number of affected cognitive domains, MCI-PD is classified into single-domain MCI-PD and multi-domain MCI-PD. First level assessment for the diagnosis of MCI-PD requires one neuropsychological test for each of the five cognitive domains, while second level assessment includes at least two tests for each cognitive domain which allows the sub-typing of MCI-PD in single-domain and multiple-domain MCI-PD [55]. It was established that multiple-domain MCI-PD occurs more frequently than single-domain MCI-PD, the most affected cognitive domains being executive, visuo-spatial, memory and attention [56]. The most common subtype of MCI-PD is the non-amnestic subtype, while speech disorders are less common [57]. MCI-PD is usually a precursor to D-PD, with 19-62% of patients with MCI-PD developing Parkinson's disease dementia within 2 to 5 years after receiving a diagnosis of MCI-PD [58]. The risk of developing D-PD in the next 5 years for patients with MCI-PD is 6.5 [59]. However, in some patients with MCI-PD cognition may be restored. According to a meta-analysis, 28% of MCI-PD patients followed-up for one year, returned to a normal cognitive state; but had a higher rate of progression to D-PD and a lower rate of return to normal cognition at a follow-up of over 3 years [60]. This fact can be explained by the "dual syndrome hypothesis" which mentions two types of MCI-PD: *MCI-PD* with predominant frontal striatal involvement and MCI-PD with predominant temporal and posterior cortical dysfunction [61]. The MCI-PD type with predominant frontal striatal involvement manifests with disfunctions related to planning, working memory and response inhibition, which are modulated by dopamine. It may be present even in the initial stages of PD and rarely progresses to D-PD. The MCI-PD type with predominant temporal and posterior cortical dysfunction presents with deficits in attention, semantic verbal fluency, and visuospatial difficulties and leads to a higher risk of developing D-PD [61].

Parkinson's disease dementia. Parkinson's disease dementia is a common late manifestation of Parkinson's disease and is characterized by a cognitive decline that is stereotyped, rapid, devastating, and has an impact on daily activities. The essence of cognitive changes in D-PD is executive dysfunction that is characterized by impaired planning, mental inflexibility, deficiencies in abstract thinking and verbal fluency, and apathy. Attention, visual-spatial functions, and memory may also be impaired, while speech is usually preserved [62]. Patients with D-PD suffer memory impairments, especially impacting rapid memory, that improve when given clues [63]. A diagnosis of D-PD is based on the presence of deficits that are severe enough to affect activities of daily living, which occur in at least two of the four basic cognitive domains (attention, memory, executive and visuospatial) [55]. D-PD is accompanied by neuropsychiatric symptoms, such as: mood disorders, psy-

chosis, and hallucinations. Visual hallucinations are usually complex, with preserved discrimination.

Assessment of cognitive impairment in Parkinson's Disease includes questioning both the patient and the caregiver [64]. It is important to understand if the person presents with a new symptom or has had problems of this kind in the past. In the case of an acute onset of cognitive decline, potential causes are evaluated, such as: infections; metabolic disorders, like the decompensation of chronic somatic diseases with renal or hepatic insufficiency; craniocerebral trauma with acute subdural hematoma; other somatic diseases with acute onset; the patient's medication (high doses of dopaminergic drugs, the use of amantadine and dopamine agonists, the use of drugs with a pronounced anticholinergic effect, both antiparkinsonian and non-antiparkinsonian). In the case of an insidious onset of cognitive decline, potential causes are evaluated, such as: coexisting cerebrovascular disease, vitamin B12 deficiency, thyroid dysfunction, craniocerebral trauma, chronic subdural hematoma, autoimmune diseases, visual or auditory sensory disorders, depression and anxiety, sleep disorders, overwork, psychosis, orthostatic hypotension associated with PD [65].

There are a series of screening tests for cognitive decline in Parkinson's disease – rating scales.

Validated scales with good inter-rater reliability are recommended for the screening of cognitive decline in PD [66]: Montreal Cognitive Assessment Scale (MoCA), Dementia Rating Scale 2 (DRS-2) and Parkinson's Disease-Cognitive Rating Scale (PD CRS) [67].

The Montreal Cognitive Assessment (MoCA) was developed as a screening test for mild cognitive impairment. It covers visual, executive, attention, memory, language, and orientation functions and can be completed in 10-30 minutes. A total score below 26 points suggests MCI-PD, and a total score below 21 points indicates D-PD [68]. The Dementia Rating Scale 2 (DRS-2) is a global test of cognitive function that assesses cognitive domains such as: attention, initiation/perseveration, construction, conceptualization, and memory. It can be performed in approximately 20-30 minutes and has cut-off scores of 139 out of 144 for MCI-PD and 132 out of 144 for D-PD [69]. The Parkinson's Disease-Cognitive Rating Scale (PD CRS) is designed for the entire spectrum of cognitive disfunctions of Parkinson's disease. It includes tasks for frontal and subcortical functions (sustained attention, working memory, alternating and action verbal fluency, clock drawing, immediate verbal recall and long-term memory) but also tasks for posterior cortical functions (clock copying) and can be completed in approximately 20 minutes. By keeping copies of previous tests – clocks, copied numbers, etc. – it's possible to monitor the evolution of cognitive performance over time. The Mini-Mental State Examination (MMSE) (traditionally used as a standard clinical test for assessing cognitive dysfunction) evaluates cortical cognitive aspects that are usually preserved in D-PD, so it is not recommended as a first-choice neuropsychological test. Screening tests of executive function are not specific, they are sensitive to the deterioration of other cognitive domains, but by using several screening tests, the pattern of cognitive deficit can be obtained.

Neuropsychological testing aims to identify the affected cognitive domains. Specific neuropsychological tests have been proposed to evaluate the different cognitive domains affected in PD. Executive function implies planning, cognitive flexibility, motor inhibition, cognitive inhibition, working memory, motor sequencing, timing, concentration/attention. Planning deficit manifests through organizational problems. It can be quickly tested by drawing the clock (circle, placing basic figures, etc.) or describing the stages of planning a trip. Cognitive inflexibility manifests as perseveration and difficulties in changing tasks. It can be quickly assessed by testing phonetic fluency (number of words beginning with "C" in 60 seconds). Motor inhibition deficits or motor inhibition errors can be highlighted by "Start! / Stop!" commands, Luria loops or Luria parapets [70]. Cognitive inhibition deficit is manifested by impulsivity, sexual disinhibition, obsessions; it can be inferred from swearing during testing of the phonemic fluency [71]. Patients with impaired working memory mention situations like: "I forgot the reason why I entered the room". This deficit can be objectified by counting forward and backward, simple calculations (addition / subtraction) [72]. Impairments in motor sequencing can manifest as difficulties in using new tools and can be objectified by the "fist-lip-palm" motor sequence repetition test. The synchronization deficit is indicated by the wrong estimation of time and can be objectified by the test of touching a surface with a finger to a certain stimulus. Patients with attention/concentration deficits often ignore road signs. This deficit can be tested by counting backwards, auditory target detection, surface touching for each 'A' in a letter sequence [72]. Visuospatial function refers to: perceptual discrimination, face recognition / discrimination, emotion recognition, spatial orientation, visual construction, visual memory. Patients with impaired perceptual discrimination may not recognize the items in a refrigerator. This dysfunction can be revealed by the "overlapping digit recognition test". Patients with face recognition/discrimination disorders are overall confused in the social environment. This disfunction can be objectified by testing the recognition of celebrities. Emotion recognition deficits can result in interpersonal difficulties and can be assessed by the ability to recognize the examiner's mimicked emotion. Spatial orientation deficit may manifest as wandering. These patients will not be able to correctly describe the route to their own home. Impairments of visual construction cause difficulties in making minor repairs or cooking. It can be objectified by the test of copying a figure. Deficits in *visual memory* can be indicated by keys or wallet misplacement and can be tested by contemplating a figure and then drawing it from memory. Episodic memory deficits in D-PD are usually mild and present

late in the course of the disease [73]. Patients with episodic memory impairment forget conversations and events. Memorizing a list of heard words with their subsequent recall, using category or multiple-choice cues for guidance, is a test that can be used to identify deficits in episodic memory. Speech is usually preserved in PD and occasional language deficits may be indicators of a superimposed dementia of neurodegenerative or vascular origin. Although the diagnostic criteria of D-PD state that basic language functions should be preserved [62], more than half of patients with D-PD also have comorbid amyloid pathology [73], and screening for these speech deficits is important for prognosis and treatment. During the general neurological examination attention is drawn to the use of nouns, repetitions, and the fulfillment of commands. Patients may show word-finding difficulties or paraphasia. Fluency tests for nouns or categories of nouns (60 seconds time allowed) or tests for completing simple commands are useful. Speech disorders, as well as episodic memory impairment in a patient with D-PD, may indicate a superimposed dementia within an associated proteinopathy (tau or ß-amyloid). The model of cognitive decline is best identified by applying standardized, validated neuropsychological tests with appropriate population norms, adjusted according to age, level of education, area [74]. Certain cognitive domains are targeted through certain neuropsychological tests: (1) Attention and working memory – the counting-back test; route making test; word-color Stroop test; WAIS-IV-number/letter sequencing; WAIS-IV-coding; (2) Executive – drawing the clock; verbal fluency test (letters, categories of objects/beings), Wisconsin / Nelson card sorting test; (3) *Speech* – WAIS-IV-similarities, Naming-matching test, Boston naming test; (4) Memory – word list learning test with delayed recall and subsequent recognition (Rey Auditory Verbal Learning Test, California Verbal Learning Test, Hopkins Verbal Learning Test, Selective Recall Test); the delayed prose-text recall test (the Wechsler Scale-IV logical memory subtest or the Rivermead paragraph recall subtest), the short visual memory test; (5) Visuo-spatial – copying the clock; the Benton test for determining the orientation of lines; the Hooper test of visual organization.

Because poor cognitive performance can be due to deficits in multiple domains, it is necessary to use multiple tests to identify the most significant deficit suggestive for a particular etiology of the cognitive impairment.

Diagnostic criteria of different degrees of cognitive decline in Parkinson's disease. To establish a diagnosis of cognitive decline associated with PD, the DSM-V criteria for diagnosing major or minor cognitive disorders associated with Parkinson's disease [75] or the criteria of the International Parkinson and Movement Disorder Society can be used.

According to the DSM-V criteria: Major or minor cognitive impairment *can be attributed* to Parkinson's disease if: it occurs within established PD; has an insidious onset and slow progression. The cognitive impairment is considered probably attributable to Parkinson's disease if: (1) there is no evidence of another disorder that could contribute to the cognitive decline, and (2) Parkinson's disease clearly precedes the onset of the cognitive impairment. Cognitive impairment is *possibly attributable* to Parkinson's disease if only one of the two criteria is met. Associated features that support the diagnosis are – apathy, depression, anxiety, hallucinations, personality changes, REM sleep behavior disorder, and excessive daytime sleepiness [75]**.** The International Society of Movement Disorders has developed diagnostic criteria for the diagnosis of Parkinson's disease-associated minor cognitive impairment MCI-PD [55] and for Parkinson's disease dementia [75]**.**

According to the International Society of Movement Disorders Criteria, the diagnosis of minor cognitive impairment associated with Parkinson's disease (MCI-PD) is established at two levels. Level I is a shortened assessment and consists of denoting the existence of cognitive deficit, according to a scale suitable for cognitive testing in Parkinson's disease (Montreal Cognitive Assessment Scale (MoCA), Dementia Rating Scale 2 (DRS-2) or Parkinson's Disease-Cognitive Rating Scale (PD CRS)) and impairment on at least two neuropsychological tests on an abbreviated assessment (one test per domain; fewer than five cognitive domains assessed). Level II is an extensive assessment, using at least 2 tests for each of the five cognitive domains (attention and working memory, executive functions, language, memory, visuospatial skills). MCI-PD can be diagnosed if there is impairment in two tests within one domain or impairment within one test in two different domains. Cognitive impairment is manifested by scores of 1–2 standard deviations below the norm, significant decline in serial tests, significant decrease in functioning compared to the premorbid level. Level II allows the identification of MCI-PD subtype: single-domain MCI-PD (impairment on two or more tests in one domain) and multi-domain MCI-PD (impairment on at least one test in two or more domains) [67]**.**

According to the International Society of Movement Disorders, the diagnosis of Parkinson's disease dementia also occurs at two levels. The first level consists of establishing a diagnosis of PD according to the UK Brain Bank criteria for PD, before the onset of dementia; a Mini-Mental State Examination (MMSE) score of less than 26; an impact of cognitive impairment on daily life that is independent of motor symptoms. Cognitive impairment must be present in more than one cognitive domain. Major depression, delirium, or other disorders that would obscure the diagnosis must be absent. *Level II* consists of an extensive assessment of four compartments: global cognitive efficiency, subcortical-frontal characteristics of D-PD, cortical characteristics of D-PD (language, visuo-constructive, visuo-spatial, visuo-perceptual) and neuropsychiatric characteristics of D-PD (apathy, depression, visual hallucinations, psychosis) [76]**.**

The differential diagnosis of Parkinson's disease de-

mentia is mainly done with Lewy body dementia and is based on an arbitrary distinction between the time of onset of motor and cognitive symptoms [77]. In Lewy body dementia, dementia precedes the development of parkinsonian motor symptoms. Lewy body dementia is diagnosed when dementia has developed within one year of the onset of motor symptoms, while D-PD is defined as dementia occurring in already established PD, with motor symptoms having lasted more than one year [78]. Both Lewy body dementia and D-PD present with neuropathological changes related to Lewy bodies [79] and have similar clinical profiles including visual hallucinations, cognitive fluctuations, and parkinsonian motor symptoms [79]. In favor of the single spectrum "Parkinson's disease dementia – Lewy body" is the fact that neuropsychological testing shows a severe deficit in executive functioning, visuospatial processing and verbal learning in both D-PD and Lewy body dementia. Lewy body dementia and D-PD are considered to represent entities within the same spectrum, with a similar pattern of impairments [31].

What is the impact of dopaminergic therapy on cognition in Parkinson's disease patients? Dopaminergic drugs can improve the performance on tasks modulated by the dorsal caudate, but they may worsen the performance on tasks modulated by the ventral striatum, due to dopaminergic deficits that are different in these regions [80]. The effect of dopaminergic drugs on executive function differs depending on the stage and severity of the disease, the dose of the drug, and the specific cognitive task assessed [81]. There is evidence of improvement of working memory, planning and behavioral flexibility in patients taking levodopa [82]. Low doses of levodopa and dopaminergic agonists cause drowsiness, while high doses of levodopa promote wakefulness and alertness [83]. Dopaminergic drugs, especially dopamine agonists, are associated with the onset or worsening of visual hallucinations in some patients with PD. However, the latency of the hallucination's onset is influenced by the mechanisms of the disease itself rather than by the dopaminergic regimen administered. Dopaminergic drugs improve cognitive flexibility, planning, working memory, attention, timing, motor inhibition, perceptual initiation and discrimination; and can worsen motor sequencing, cognitive inhibition, visual memory and emotion recognition [84].

The choice of initial medication at the onset of PD – levodopa, or a dopamine agonist, or a monoamine oxidase-B inhibitor, was found to make no difference to the cumulative rates of dementia [85]. However, drugs with strong anticholinergic properties (for PD (benztropine, trihexyphenidyl) or for issues other than PD) are associated with worse long-term cognition, both in the general population and in PD patients, especially in the cases of a long-term exposure to several anticholinergic drugs or to a drug with more pronounced anticholinergic properties [86]. In patients with PD and comorbid psychosis, it is necessary to simplify antiparkinsonian treatment by gradually stopping non-levodopa antiparkinsonian drugs, in the following order: anticholinergic drugs, amantadine, selegiline, dopaminergic agonists, COMT inhibitors [87].

Several studies have found that deep brain stimulation can worsen cognitive function [88]. Continuous dopaminergic stimulation, such as continuous subcutaneous infusion of apomorphine and intrajejunal infusion of levodopa (IJL), was previously avoided in patients with PD-related cognitive impairment. Currently, continuous subcutaneous infusion of apomorphine is considered for patients with MCI, while intrajejunal infusion of levodopa is considered for patients with MCI and mild-moderate D-PD [89]. Continuous dopaminergic stimulation could especially benefit patients with cognitive complaints as a manifestation of non-motor fluctuations [90].

Management of cognitive impairment in Parkinson's disease. The optimal management of cognitive impairment in PD is a multidisciplinary approach, with pharmacological, non-pharmacological and psychosocial strategies. It begins with assessing the presence, severity, and impact of cognitive impairment, as well as investigating factors that contribute to cognitive decline: comorbidities, medications, modifiable risk factors. Counseling patients and families and developing a management plan is essential. Adequate management is required for orthostatic hypotension associated with advanced PD, cerebrovascular disease and vascular risk factors (diabetes mellitus, obesity, hypertension, arrhythmia), alcohol consumption, depression and associated sleep disorders [19]. Neuroimaging is useful for identifying structural etiologies (stroke, chronic subdural hematoma, intracerebral neoplasm) [31], and laboratory examinations – for diagnosing systemic infections or metabolic abnormalities (hypothyroidism, vitamin B12 or vitamin D deficiency) [31].

Pharmacological treatment of cognitive decline associated with Parkinson's disease. If the patient presents with psychosis and hallucinations, the first step is to rule out secondary causes – infections or toxic-metabolic etiologies. The next step is to stop administering non-essential non-parkinsonian drugs – anticholinergics, benzodiazepines, opioids. Subsequently, a reduced and simplified parkinsonian treatment is considered [91]. If optimal improvement of psychotic symptoms still does not occur, an atypical antipsychotic may be added. However, acetylcholinesterase inhibitors have been proposed by some authors for the management of psychosis and hallucinations as a step preceding antipsychotic drugs. To date, only rivastigmine has been approved for the treatment of D-PD [92]. There is insufficient evidence for the use of acetylcholinesterase inhibitors in MCI-PD [93].

Non-pharmacological management of cognitive impairment in Parkinson's disease. Non-pharmacological interventions for D-PD and MCI-PD include psychological rehabilitation, cognitive training, exercise, music, art therapy and non-invasive brain stimulation techniques [94].

Neuropsychological rehabilitation comprises the use of

cognitive and behavioral psychological interventions and includes educational, psychotherapeutic and motivational components, as well as "exercises" to activate specific cognitive functions [84]. Neuropsychological rehabilitation protocols include common goals (applicable to most patients, like the management of stress, sleep disturbances, limited social stimulation [84]; and specific goals (applicable to a particular patient), which are identified as a result of neuropsychological assessment and discussions with the patient and family which refer to interventions, such as not to lose certain objects around the house or organizing tips in order not to miss meetings, etc. Cognitive-behavioral therapy (CBT) aims to modify cognition and behavioral routines [95]. Optimizing cognitive function is achieved indirectly through physical exercise, proper sleep hygiene, adaptive stress management, social engagement, and continuous cognitive stimulation. Problems are identified jointly by the CBT provider, patient, and family. The final goal is the awareness of the negative influence of some harmful routines on the motor and cognitive symptoms of the disease and their optimization. Cognitive training improves global cognition, working memory, executive function, processing speed and attention. This is achieved through different types of tasks: computer programs, arts, crafts, reading, puzzle games, card games or board games [84]. Several randomized clinical trials stipulate significant positive effects of aerobic and resistance exercise on cognitive function in patients with D-PD [96]. Tango, cognitive training combined with motor training and treadmill training have positive effects on global cognitive function, processing speed, sustained attention and mental flexibility [97]. Compensatory strategies and devices – the most direct and practical method of addressing problems arising from cognitive deficiencies – refer to: drawing up lists of activities to be performed or objects to be purchased, using diaries for noting activities in advance, implementing organizers for drugs, alarms for finding objects.

An important aspect of neuropsychological rehabilitation, as part of the multimodal management of cognitive impairment in PD, is the patient's involvement in his own care, giving him a sense of self-control in dealing with his own illness. In this case, all these interventions will have the potential to have a significant impact on the patient's functionality and quality of life.

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Authors' contribution

LR, OG conceptualized the idea, conducted literature review, wrote the manuscript; SG revised and finalized the text. All the authors revised and approved the final version of the manuscript.

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