Chapter 2
Mild Cognitive Impairment in Parkinson's Disease

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Abbreviations

AD	Alzheimer's disease
DLPFC	Dorsal lateral prefrontal cortex
MCI	Mild cognitive impairment
OFC	Orbitofrontal cortex
PD	Parkinson's disease
PFC	Prefrontal cortex

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Introduction

Motor features such as resting tremor, bradykinesia, or postural instability historically characterized Parkinson's disease (PD). However, compelling evidence proved that cognitive impairment is also pervasive in PD, constituting a clinical characteristic of the disease [1]. Cognitive impairment in PD can be identified as both minor cognitive defects—present in up to 30 % of patients at time of diagnosis—and up to dementia [2]. In fact, in cross-sectional studies dementia is seen in more than 20 % of PD patients [3] and shows a cumulative prevalence up to 80 % after 20 years of follow-up [4–8].

Although the trajectory of cognitive impairment is variable along the course of the disease, these alterations have a high impact on the quality of life of the patients and on caregiver distress [9–11]. While most PD subjects exhibit relatively subtle cognitive deficits when compared with controls, [2] an intermediate transitional state of mild cognitive impairment (MCI) has been defined and suggested to be a predictor of further development of PD dementia (PDD) [3, 12, 13]. Given that PD supposes a four to six times greater risk of developing dementia, the definition and identification of neurocognitive predictors of PDD currently constitutes one of the major topics of interest in PD research. Henceforth, whether different profiles of early cognitive alterations in non-demented patients have different prognostic implications still remains to be determined [13, 14].

Unlike the construct of MCI in the general population considered as prodromic of Alzheimer's disease (AD) [15], MCI in PD (PD-MCI) must not necessarily announce short-term dementia [6, 16]. With a relative independence on the degree of early cognitive alterations seen in most of the patients from the beginning of the disease, some patients rapidly convert to dementia, while others remain stable for years [17].

This emphasized the need: (a) for a better understanding of the underlying mechanisms of early cognitive alterations in PD, (b) to define standardized methods for cognitive assessment, and (c) to determine the prognostic implications of specific cognitive profiles [13, 16].

Along this chapter we will describe the concept and underlying mechanisms of PD-MCI, the recommended evidence-based methods to assess early cognitive alterations and the clinical and prognostic implications of the different cognitive profiles that can be recognized as PD-MCI. Thus, we will review current and validated measures for cognitive assessment in PD, the methods to determine whether a cognitive performance pattern represents a decline from the previous level or current expected level, and the methods to assess the impact of cognitive abilities over activities of daily living.

Cognition in Parkinson's Disease

Cognitive impairment is intrinsic to PD [2]. From the earliest stages of the disease, patients suffering from PD may exhibit some degree of cognitive alterations [4, 18]. These early cognitive alterations seen in up to 80 % of PD patients at time of diagnosis resemble those observed in patients with lesions involving the prefrontal cortex

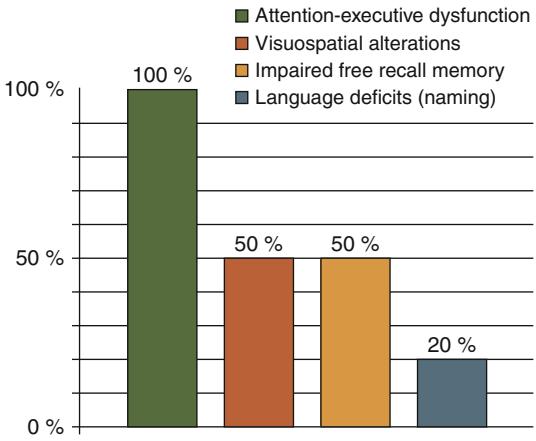

Fig. 2.1 Cognitive profile of patients with newly diagnosed PD [2]

(PFC) [19, 20] (Fig. 2.1). Thus, cognitive impairment in PD is mainly characterized by defects on executive functions such as alterations in working memory, cognitive flexibility, planning, and attention [2, 16, 19]. However, when cognition is adequately explored, alterations involving other cognitive domains—such as memory and visuospatial/visuoconstructive functions—can be seen accompanying executive dysfunction in up to 50 % of the patients [2, 3].

Cognitive changes seen in PD probably have a multifactorial causality with the pattern of observed deficits varying in accordance to the progressive course of the pathologic and neurochemical changes of the disease [21]. Most of the frontal-executive deficits seen in PD are closely related to the progressive dopaminergic depletion that occurs in the early stages of the disease [22–24]. Accordingly, the main neuropsychological profile of PD has been classically defined as a predominant "frontal-subcortical" syndrome with preserved performance on instrumental tasks, the latter considered to be specific to neurodegenerative diseases with a cortical involvement such as AD [19, 20]. Nevertheless, it is currently known that up to 20 % of non-demented PD patients can also exhibit alterations in tasks mainly involving posterior-cortical functions such as encoding information, confrontation naming, or picture copying [2, 21, 25, 26]. Thus, it was proposed that the transition from PD-MCI to PDD appears characterized by a pattern of significant addition of this kind of AD-like cognitive alterations [6, 12, 25, 26]. This emphasized the need for accurate and standardized methods for cognitive assessment in PD to better clarify whether cognitive alterations evidenced at a given time point of the disease might be taken as consistent markers of conversion to dementia [27].

The Role of Dopamine in Cognitive Impairment in PD

The involvement of dopamine in high-order cognition has been largely supported by numerous studies [24]. The massive number of dopaminergic projections emerging from the PFC to the caudate nucleus and the reciprocal

Table 2.1 Effects of dopaminergic replacement therapy over cognitive functions in PD [42]

Cognitive benefit
Set shifting
Working memory
Spatial working memory
Cognitive deterioration
Concurrent learning
Probabilistic reversal learning
Decision making
Visual hallucinations
No effect
Attentional set shifting
Task switching-abstract rules
Pattern and spatial recognition memory
Associative learning
Verbal memory

Adapted from Kehagia et al. [42], with permission

striato-pallido-thalamo-cortical projections to the PFC through the basal ganglia indicates the importance of the frontal-subcortical systems over cognition [22, 28, 29]. In humans, well-differentiated frontal-subcortical circuits emerge from different portions of the striatum establishing connections with segregated regions of the PFC [30–32]. Thus, while dorsal caudate nucleus mainly projects to dorsal lateral PFC (DLPFC), the ventral striatum projects to medial and orbital PFC (mPFC; oPFC), anterior cingulate cortex (ACC), and limbic system [22, 33, 34].

During the earliest stages of PD, massive loss of dopaminergic neurons mainly disrupts both motor putamen and dorsal caudate [22, 29, 33–35]. Lack of coactivation of the striatum with functionally related DLPFC is critical in the development of executive defects [35, 36]. These functional defects characteristic of early cognitive impairment in PD resemble those presented by patients suffering from conditions with structural involvement of the DLPFC [24, 36]. This dopaminergic dependence of frontal-executive functions in PD supports the remediation or improvement seen on the performance of some frontal-related tasks after initiation of dopaminergic replacement therapy [37–39] that partially compensate the dorsal caudate dopaminergic deficiency [35, 40].

However, a paradoxical cognitive effect also mediated by the treatment with dopaminergic drugs can be seen in PD and explains the occurrence of other cognitive alterations (Table 2.1). As indicated, dorsal caudate projections are known to be significantly impaired from the earliest stages of the disease. However, the ventral striatum and its related projections are known to remain relatively spared during the early and middle stages of the disease [33, 34]. Thus, the doses of dopaminergic drugs used to remediate the motor alterations of PD related to dopaminergic deficiency in the putamen result excessive and lead to an overdose of other unaffected or less dopamine-depleted regions [35]. Consequently, those cognitive functions more

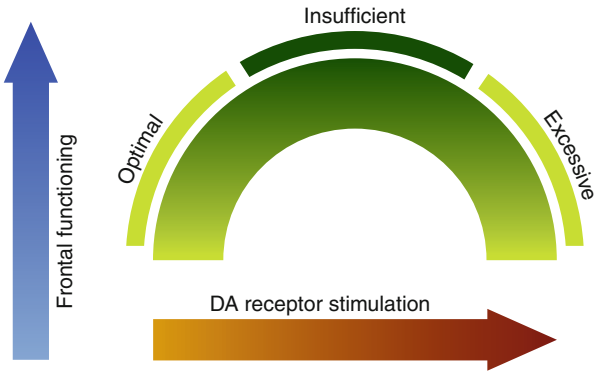

Fig 2.2 Effect of dopaminergic replacement therapy over frontal functions

dependent on ventral striatum projections to orbital and medial PFC that appeared intact before initiation of dopaminergic replacement therapy (i.e., decision making, reversal learning) tend to appear altered, while those more dependent on dorsal caudate projections to DLPFC previously altered show consistent improvement [35, 38, 40–42]. This inverted-U relationship (Fig. 2.2) has been demonstrated in numerous controlled studies, indicating that cognitive alterations seen in PD may variably depend on dopaminergic depletion and neurodegeneration, disease staging, and dopaminergic overdose over spared regions [34, 38].

The paradoxical dopamine-dependent response demonstrates the fragile relationship between optimum levels of dopamine and cognition [38, 40, 41] which should be taken into account when assessing cognitive functions in PD.

The Role of Acetylcholine in Cognitive Impairment in PD

While most of the cognitive defects initially seen in non-demented PD can be understood within the framework of frontal-executive alterations fueled by dopaminergic deficits, not all the cognitive alterations seen in early PD respond to dopaminergic replacement therapy. This suggests that other neurotransmitters are involved on the pathogenesis of cognitive impairment. Loss of cholinergic cells at the basal nucleus of Meynert (bNM) and pedunculopontine nucleus (PPN) is also known to be present in PD [43, 44]. Alterations on the cholinergic projections have been consistently related to cognitive deterioration in PD [23]. Alterations in cognitive domains such as visuospatial and visuoconstructive skills or memory, that do not significantly ameliorate after initiation of dopaminergic replacement therapy, may obey to cortical cholinergic deficit [23, 25, 45]. In this line, disregarding disease duration, cholinergic depletion in patients presenting dementia associated to PD (PDD) is comparable to that observed in patients with Lewy body dementia [46]. It was suggested that the

conversion of PD-MCI to PDD, signaled by the addition of significant neuropsychological deficits related to posterior cortical dysfunction (i.e., visuospatial or language defects), is related to progressive cholinergic deficit [6, 14, 47–49]. Accordingly, PD-cholinergic alterations and related cognitive impairment seem to be more relevant than dopamine-dependent features on the definition of the prognostic implications of a given cognitive profile [13].

In line with the recent formalization of the clinical criteria for both PDD and PD-MCI [50, 51], many studies have been developed on the topic of identifying the neurobiological correlates of cognitive deterioration in PD. Severe dopamine deficits have been emphasized to follow the emergence of cognitive alterations. However, alpha-synuclein pathology followed by limbic and cortical loss of dopamine, noradrenaline, serotonin, and acetylcholine neurons has been significantly pointed as added mechanisms leading to cognitive deterioration and dementia in PD [33, 52]. In addition, genetic factors such as triplications in the alpha-synuclein gene or MAP-t haplotypes have been also linked to cognitive decline [53, 54].

Parkinson's Disease Mild Cognitive Impairment: Definition and Clinical Implications

The concept of mild cognitive impairment (MCI) was defined in the field of AD indicating the transitional stage between normal cognition and dementia [55]. Thus, mild cognitive impairment (MCI) refers to the stage between normal aging and dementia [56] and was originally used to describe prodromal AD. More recently, MCI has become important in studies on PD, [57] where it is called MCI in PD (PD-MCI) [50]. Whereas MCI due to AD is primarily characterized by memory impairment, cognitive deficits of PD-MCI in newly diagnosed patients more often concern a range of cognitive domains, including memory, visual-spatial, and attention/executive abilities [2, 4].

AD-MCI occurs when, in the presence of significant and measurable cognitive alterations in one or more cognitive domains, independent activities of daily living (IADL) are preserved. In the field of AD, diagnosis of MCI should be unequivocally linked to a progressive linear worsening leading to dementia [15]. More specifically, it is known to occur in those patients presenting an amnesic type of MCI. However, this concept pointing for a transitional stage towards dementia results more complex when it refers to PD [16, 58]. In the context of PD, most patients present relatively mild but significant cognitive alterations since the beginning of the disease, and there is an unclear relationship between the occurrence of these symptoms and unequivocal transition to dementia [14, 18].

Epidemiological studies have demonstrated that from the beginning of the disease to more advanced stages, the cognitive profile of PD patients is largely heterogeneous (Table 2.2) [2–4, 13, 18, 50, 59, 60]. Hence, the prospective Sydney Multicenter Study [8] identified three cognitive phenotypes in PD: (i) PD patients with early and prominent dementia clinically corresponding with dementia with

Table 2.2 Studies of prevalence and MCI subtypes in PD [2, 3, 5, 13, 18, 57, 59, 60]

Authors	Year	Sample size	Disease duration	PD-MCI (%)	PD-MCI type (%)
Muslimovic et al. [2]	2005	115	1.6	24 %	Múltiples dominios
Janvin et al. [13]	2006	72	11	52 %	44 % non-amnesic single domain
					39 % multiple domains
					15 % amnesic single domain
Caviness et al. [3]	2007	86	9.2	21 %	39 % non-amnesic single domain
					22 % non-amnesic multiple domains
					22 % nmnesic single domain
Aarsland et al. [18]	2009	196	2.4	18.9 %	62.2 % non-amnesic single domain
					2.7 % non-amnesic multiple domains
					24.3 % amnesic single domain
					10.8 % amnesic multiple domain
Aarsland et al. [5]	2010	1,346	6.1	26 %	11.3 % non-amnesic single domain
					8.9 % amnesic single domain
					4.8 % amnesic multiple domain
					1.3 % non-amnesic multiple domain
Litvan et al. [57]	2011	776	ND	26.7 %	Non-amnesic more frequent tan amnesic in 8 reviewed studies
Goldman et al. [59]	2012	125	7	ND	47.7 % non-amnesic single domain
					24.2 % amnesic single domain
					18.8 % non-amnesic multiple domain
					9.5 % no amnésico múltiples dominios
Yu et al. [60]	2012	94	4.4	46.8 %	25.5 % non-amnesic single domain
					7.4 % non-amnesic multiple domains
					7.4 % amnesic multiple domain
					6.4 % amnesic single domain

Levy bodies, (ii) older patients (>70 years old) developing dementia after 3–10 years clinically corresponding to PDD, and (iii) a younger group who may remain cognitively intact during many years and eventually develop dementia at a given point [17, 18]. As a result, main interest relates on whether it is possible to differentiate these early cognitive profiles predicting a benign or relatively slow course to those with a more malignant course to dementia [6, 12, 25, 61].

As previously stated, an estimated 15–20 % of non-demented PD patients also exhibit deficits in more cortical-dependent tasks such as confrontation naming or encoding deficits [2, 3, 13]. This pattern of added posterior-cortical alterations is commonly evidenced in patients who convert to PDD [12, 21, 27]. Notably, while the progression of frontal-executive deficits usually follows a slow and linear decline, the addition of posterior-cortical alterations occurs in an abrupt nonlinear and faster fashion [6, 27].

The importance of exploring for posterior cortical defects as possible prodromal markers of dementia is highlighted by the fact that even in drug-naïve PD patients with mild cognitive impairment (PD-MCI), decline in executive/attentional, visuospatial, and memory functions appeared directly related to cortical hypometabolism in prefrontal but also in posterior cortical networks. Such pattern is shared in advanced stages of PD-MCI and PD with dementia [62, 63].

Given the proposed heterogeneity on both clinical characteristics and prognostic implications of PD-MCI, a task force commissioned by the Movement Disorders Society (MDS) recently established the diagnostic criteria for MCI in PD (PD-MCI) [50]. These criteria (Table 2.3), based on literature review and expert consensus, presuppose that PD-MCI might also be associated with impairments in daily functioning and quality of life. The criteria are presently under validation and are open to modification when further research improves knowledge of the clinical syndrome of PD-MCI and its subtypes [4, 18, 26, 27].

Neuropsychological Assessment of Cognitive Impairment in PD

Per definition, neuropsychological assessment methods differ from other specialties—such as cognitive neurology or neuropsychiatry—by the use of standardized, quantitative, and norm-referenced procedures [64]. Clinical neuropsychology provides clinicians and researchers with a large list of standardized and normalized assessment tools able to cover for all the cognitive domains of interest when assessing cognitive status in PD. However, test selection on the setting up of comprehensive neuropsychological assessments should be always done taking into account the study population of interest (i.e., AD, PD, traumatic brain injury) and the information that will be provided by the tools employed (i.e., global cognitive status addressed through screening methods, detailed cognitive performance at different

Table 2.3 Diagnostic criteria for PD-MCI [50]

Inclusion criteria
Diagnosis of Parkinson's disease as based on the UK PD Brain Bank Criteria
Gradual decline, in the context of established PD, in cognitive ability reported by either the patient or informant, *or* observed by the clinician
Cognitive deficitcis on either formal neuropsychological testing or a scale of global cognitive abilities
Cognitive deficits are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present
Exclusion criteria
Diagnosis of PD dementia based on MDS task force proposed criteria
Other primary explanations for cognitive impairment (e.g., delirium, stroke, major depression, metabolic abnormalities, adverse effects of medication, or head trauma)
Other PD-associated comorbid conditions (e.g., motor impairment or severe anxiety, depression, excessive daytime sleepiness, or psychosis) that, in the opinion of the clinician, significantly influence cognitive testing
Specific guidelines for PD-MCI level I and level II categories
A. Level I (abbreviated assessment)
Impairment on a scale of global cognitive abilities validated for use in PD *or*
Impairment on at least two tests, when a limited battery of neuropsychological tests is performed (i.e., the battery includes less than two tests within each of the five cognitive domains, or less than five cognitive domains are assessed)
B. Level II (comprehensive assessment)
Neuropsychological testing that includes two tests within each of the five cognitive domains (i.e., attention and working memory, executive, language, memory, and visuospatial)
Impairment on at least two neuropsychological tests, represented by either two impaired tests in one cognitive domain or one impaired test in two different cognitive domains
Impairment on neuropsychological tests may be demonstrated by:
Performance approximately 1–2 SDs below appropriate norms *or*
Significant decline demonstrated on serial cognitive testing *or*
Significant decline from estimated premorbid levels
Subtype classification for PD-MCI (optional, requires two tests for each of the five cognitive domains assessed and is strongly suggested for research purposes)
PD-MCI single-domain—abnormalities on two tests within a single cognitive domain (specify the domain), with other domains unimpaired *or*
PD-MCI multiple-domain—abnormalities on at least one test in two or more cognitive domains (specify the domains)

Diagnostic criteria for PD-MCI from the Movement Disorders Society Task Force guidelines [50]

cognitive domains, detailed performance in a specific subprocess involved in a given cognitive domain) [64].

In the context of PD, assessment of cognitive status can be performed with clinical and/or research interests [25]. In both contexts, accurate neuropsychological assessment must be defined based on the accomplishment of psychometric standards

with a relatively independence on the effect that motor symptoms might exert over cognitive performance. However, focusing on clinical or diagnostic proposes, test selection must be done in accordance of the capacity of the tools employed to identify whether or not the patient fulfills the proposed diagnostic criteria for PD-MCI or PDD [25, 50].

On the context of screening and diagnosis of PD-MCI, the selection of the tests to be used should be made on the basis of covering for all the cognitive domains of interest [25, 50, 57, 65]. It should be also taken into account that the assignment of specific cognitive tasks to single domains is a bit arbitrary. Some tests may cover more than one domain (e.g., the Rey-Osterrieth Complex Figure Test, widely used for the evaluation of visuospatial constructional ability and visual memory and also a useful tool for measuring executive function); then the intervention of an experienced neuropsychologist is highly recommendable for the selection of the instruments to be used.

As previously pointed out, from a clinical perspective, neuropsychological assessment can be constructed on the basis of allowing clinicians to determine if a given patient is fulfilling diagnostic criteria for PD-MCI and also to identify the cognitive profile [50, 66]. Thus, based on the previous described characteristics that differentiate the prognostic implications of frontal-subcortical to posterior-cortical alterations and the need to cover a full range of possible alterations, patients should be assessed in different cognitive domains [25].

Numerous cognitive assessment approaches are currently available. As noted, the preliminary consideration on test selection refers to the psychometric properties of the test. Thus, beyond the existence of good normative data, how free of producing random and nonrandom errors is the test, how well it measures and predicts all for what it was designed and how practice modulates performance.

Once focused on clinical cognitive assessment, a first approach should be done as a preliminary screening method to generally determine whether or not some degree of cognitive impairment is significantly present. Screening methods, also known as “Level 1” tests, allow a first approach to the global cognitive status of the patient and serve for the screening of PD-MCI [50]. For research purposes and formal diagnosis of PD-MCI, it is recommended to use “Level 2” tests. These latter refer to both specific neuropsychological assessment batteries compiled in order to provide an in-depth assessment of at least five cognitive domains (attention, memory, executive functions, language, and visuoperception/visuoconstruction). Thus, comprehensive neuropsychological assessment allows (a) the formal diagnosis of a given cognitive syndrome; (b) the identification of specific cognitive profiles; and (c) the reliable measurement of follow-up changes.

Functionality and day-to-day activities are also a key feature to be assessed in the context of the neuropsychological evaluation [67]. Specifically, both motor and cognitive features can independently disrupt independence on ADL. Thus, functional scales to be used should be selected on the basis of covering for the impact of cognitive—rather than just motor—alterations over functionality that may cause a significant impact on instrumental activities of daily living (IADL).

Tools for Cognitive Assessment in PD

Level 1 Tests

The Mini-Mental State Examination (MMSE)

The MMSE [68] is a general screening instrument for cognitive impairment. It can be easily and rapidly performed by a clinician and is currently the most commonly used screening test for dementia. Dependence of the MMSE on age and educational level hinders the use of a rigid cutoff score. In elderly populations, the MMSE demonstrates floor effects in subjects with severe cognitive impairment and ceiling effects in subjects with mild cognitive impairment.

It was widely used in PD as a screening tool, despite that it was not designed nor validated to assess cognitive impairment and dementia in PD. Although widely used, the Mini-Mental State Examination (MMSE) does not capture domains germane to PD (i.e., executive dysfunction) and suffers from ceiling effects (i.e., a normal score does not rule out cognitive disturbances or dementia in PD). In conclusion, the MMSE is not a recommended instrument to be used in the screening of PD-MCI [25, 50].

The Montreal Cognitive Assessment (MoCA)

The MoCA [69] was initially developed as a brief screening assessment for MCI in AD with the intention to address the limitations of the MMSE. Interestingly, the MoCA divides subscores in visuospatial/executive, language, memory, attention, abstraction, and orientation and sums an extra point when years of education are below <12 years. However, the validity of the MoCA in PD has not been unequivocally established against formal criteria or a comprehensive neuropsychological battery used to provide a criterion standard diagnosis of MCI and dementia. In a study comparing the accuracy of MMSE versus MoCA in PD patients with MCI or dementia, a cutoff score <26 was proposed for screening of MCI. When compared with the MMSE, the MoCA appeared to be more sensitive to mild frontal-subcortical cognitive defects. However, its substandard accuracy in diagnosing PD-MCI (sensitivity = 0.83, specificity = 0.53) cast some doubts on recommending this scale in PD-MCI as a useful tool other than for screening purposes [70, 71]. A MoCA cutoff point of 26 that has been established as optimal for screening cognitive impairment in PD was mostly established on how it relates to MMSE performance. Nevertheless, a positive screen using either instrument requires additional assessment due to suboptimal specificity at the recommended screening cutoff point [71, 72]. In a more recent study, the optimal MoCA screening cutoffs differed significantly, with a proposed score of <26 for PD-MCI, with sensitivity 90 % and specificity 75 %. Although the accuracy of MoCA in this study is clearly better, a specificity <80 % for screening PD-MCI is still of doubtful usefulness in clinical practice. While the MoCA still requires further study of its diagnostic utility in PD populations, among the brief tests of level 1, it can be considered a minimum cognitive screening measure in clinical trials of PD. Its value as outcome measure was not established yet.

Mini-Mental Parkinson (MMP)

The MMP [19] is a brief screening instrument derived from the MMSE initially oriented to patients who need a more comprehensive cognitive assessment. It includes seven-ordered sections assessing orientation, visual registration, attention, verbal fluency, visual recall, set shifting, and concept processing. Limitations of the scale include heavy representation of the orientation item (10 of 32 points), which is also the item contributing least to scale variance, and a lack of cortical items. The MMP also differs significantly between different stages of the disease [73].

The MMP was not subjected to an extensive clinimetric evaluation, and data is lacking regarding internal consistency, test-retest, or inter-rater reliability. In a recent work, the psychometric and validity properties of the MMP were evaluated in 69 cognitively intact and 52 cognitively impaired PD patients, classified according to their performance at the Dementia Rating Scale. The MMP showed better metrics and convergent validity and higher screening ability. However, its performance was not fully satisfying in terms of data distribution, coefficient of variation, and specificity, and ROC curves did not show clear cut superiority of either scale at their best sensitivity-specificity trade-off. The MMP seems to be slightly preferable to the MMSE only at a cutoff that favors sensitivity with respect to specificity, for screening purposes. The test is simple and quick, but has limitations in terms of validity [73].

PDD-Short Screen

The PDD-Short Screen (PDD-SS) [74] was designed and validated as a PD-specific brief cognitive test for screening dementia in PD. Based on regression analyses, and from an initial version covering different cognitive domains, a final brief version taking from 5 to 7 min to be administered disclosed a high accuracy in screening PDD. The final version included tasks assessing verbal fluency, free-recall verbal memory, clock copying, and a questionnaire on cognitive and associated psychiatric symptoms in PD. Score ranges from 0 to 22 points. ROC curves showed that a cut-off score $\leq$11 on the PDD-SS yielded high sensitivity (89.8 %), specificity (88.5 %), and positive and negative predictive values (PPV 80.7 %, NPV 93.6 %) for screening PDD. Although the accuracy for PDD was similar to that found with the Mattis Dementia Rating Scale, no further studies were still conducted to address the question of whether or not it is a feasible method for the screening of PD-MCI.

Clinical Dementia Rating Scale (CDR)

The Clinical Dementia Rating (CDR) [75] scale was developed to distinguish between normal cognition (CDR = 0), questionable dementia (CDR = 0.5), and mild, moderate, or severe dementia (CDR = 1–3). Employing a semi-structured interview, the CDR is a global rating device for assessing stages of dementia. It measures cognitive function across six domains: memory, orientation, judgment

and problem solving, community affairs, home and hobby, and personal care. Information collected by the CDR allows assessment of cognitive impairment without reference to psychometric performance. The CDR has been used in patients with PD and has been shown to be sensitive to very mild cognitive impairment [27]. Relative to healthy control subjects, subjects with PD and questionable dementia (CDR = 0.5) exhibited impairment on all psychometric measures examined, except digit span and word fluency. Quantitative impairments detected during psychometric assessment of a group of PD patients with a CDR score of 0 were not detected by the physician. This observation suggests that screening for PD-MCI using the CDR still depends on information provided by patients and caregivers and on the subjective impression of the examiner. When applied in PD, the description of progressive memory loss is ambiguous; the orientation task is not useful in differentiating between PD patients with no or very mild cognitive impairment because this cognitive function is generally not altered in PD until moderate or severe dementia appears. In addition, scoring in the items "community affairs," "home and hobbies," and "personal care" is clearly influenced by PD motor symptoms.

The Frontal Assessment Battery

The FAB [62] is a short, bedside, cognitive battery assessing frontal lobe function. It comprises six subtests mainly exploring cognitive functions mediated by the medial prefrontal cortex: conceptualization/similarities, verbal fluencies, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy. It was validated in normal control subjects and in patients with frontal lobe dysfunction (PD, multiple system atrophy, corticobasal degeneration, frontotemporal dementia (FTD), and progressive supranuclear palsy (PSP)). The FAB can be considered a useful scale to capture the cognitive impairment characteristic of pathologies with predominantly medial-prefrontal dysfunction. In PD, the FAB correlates well with measures of executive functions. The FAB does not cover for the full spectrum of cognitive impairment in PD [21, 25]. No formal studies assessed the discriminative properties of the FAB in screening or diagnosing of PD-MCI.

Level 2 Tests

The Mattis Dementia Rating Scale

Compared with the Mini-Mental State Examination (MMSE), the MDRS [76] is a more sensitive tool to detect frontal lobe dysfunction in PDD. In PD, it also accounts for more variation in the level of cognitive function. The MDRS appears to be valid and reliable; however, the first reported study attempting to validate this tool as a screening test for cognitive impairment in PD only included 14 patients. Most of the

sample showed no cognitive deficits, and no cutoff scores were provided to differentiate between the cognitive groups. A main limitation of the MDRS is length, as the estimated administration time in the general population is 20–45 min. Normative data indicates that performance on the MDRS is largely influenced by both age and educational level. When using standard diagnostic criteria for diagnosing PD-MCI, a recent paper found different cutoff scores on regard the purposes of the assessment. Thus, ≤140 and ≤137 appeared as the more accurate cutoff scores for screening and diagnostic purposes, respectively. However, an in-depth examination of sensitivity/specificity for the screening cutoff revealed that a ≤139 yielded a better balance between sensitivity (77 %) and specificity (65 %).

While some limitations of the MDRS are the relatively weak coverage of visuospatial function and language, these recent data suggest that this instrument can be used both, for a preliminary screening (cutoff ≤139) and classification purposes on research (cutoff ≤137) [77].

SCOPA-COG (Scales for Outcomes of Parkinson's Disease-Cognition)

The SCOPA-COG was developed to specifically assess cognitive defects in PD [78]. Administration takes 10–15 min and the scale demonstrated good clinimetric properties. The main known limitation of the scale is that it mostly includes items assessing frontal-subcortical functioning (orientation, attention, memory/learning, executive functions, visuospatial functions, thinking, and reasoning), but there are no items assessing instrumental-cortical functions. Accordingly, the exclusive use of this scale for the assessment of longitudinal changes in PD might be inappropriate by an insufficient identification of subgroups of non-demented PD patients with posterior-cortical patterns of cognitive impairment suggesting an increased risk of dementia [25]. Accounting for these limitations, it is a good instrument to be used in both clinical and research settings.

PANDA (Parkinson Neuropsychometric Dementia Assessment)

The PANDA [79] is a short test (8–10 min) designed to screen for cognitive impairment in PD. It includes items covering distinct cognitive domains (immediate and delayed recall memory, verbal fluency, visuospatial skills, attentions, and working memory). Despite the validation study showed appropriate discriminative properties between controls, PD, PD-MCI, and PDD patients, it was not subjected to an extensive clinimetric evaluation. As it occurs with other tools developed following the concept of cognitive impairment in PD as a predominant dysexecutive syndrome, it was eminently addressed to assess frontal-subcortical functions but does not include any item assessing instrumental-cortical functions. Nevertheless, PANDA shows superiority against the MMSE on detecting cognitive impairment in PD.

PD-CRS (Parkinson's Disease-Cognitive Rating Scale)

The PD-CRS [27] is a new instrument specifically designed to capture from subtle, mild, to major cognitive defects appearing along the course of PD. The PD-CRS displayed very good clinimetric properties, and its time of application is relatively short (ranging from 15 min in non-demented to 26 min in PDD). The PD-CRS consists of nine tasks differentially assessing frontal-subcortical and instrumental-cortical functions. The seven frontal-subcortical tasks include sustained attention, working memory, alternating and action verbal fluency, clock drawing, and immediate and delayed free-recall verbal memory. The two instrumental posterior cortical items include confrontation naming and copying a clock. In the validation study, it showed a very good power differentiating cognitively intact PD patients from both PD-MCI and PDD. As expected, instrumental-cortical items selectively differentiated PDD from non-demented PD patients. A total score of ≤64 yielded high sensitivity (94 %), specificity (94 %), positive predictive value (PPV) (91 %), and negative predictive value (NPV) (96 %) for screening PDD. These data were confirmed by an independent evaluation of the psychometric attributes of the PD-CRS that found that the scale displayed satisfactory levels of acceptability, internal consistence, construct validity, and precision [69]. The PD-CRS is a recommended instrument by the MDS task force on MCI for the evaluation of PD-MCI. Recent findings highlighting the early involvement of posterior cortical regions in PD patients with cognitive deficits and the probable relevance of this pattern in predicting prodromal dementia [21, 26] stress the additional advantage of the PD-CRS relative to other instruments in distinguishing frontal-striatal and posterior cortical patterns of cognitive impairment. A recent validation study indicated that a score ≤81 of 134 was the optimal cutoff point on the total score for the PD-CRS (sensitivity, 79 %; specificity, 80 %; positive predictive value, 59 %; negative predictive value, 91 %). In addition, a range of change from 10 to 13 points on the PD-CRS total score appeared indicative of clinically significant change [69].

Cambridge Cognitive Assessment (CAMCOG)

This is the cognitive section of the Cambridge Examination of Mental Disorders. Validation studies showed the CAMCOG as a valid and reliable scale for assessing cognitive function and screening for dementia in elderly populations [80]. It includes eight subscales: orientation, language, recall and recognition memory, attention, calculation, praxis, and perception. While the CAMCOG showed extremely good clinimetric properties for the diagnosis of PDD, no validation studies were done on the context of usefulness of CAMCOG for the screening and diagnosis of PD-MCI. In addition, disadvantages of the CAMCOG are lengthy administration time (25–30 min), and aging associated with significantly poorer scores.

Recommendations for the Interpretation of Test Results

Measurement of whether or not a given cognitive performance pattern represents a significant decline on premorbid competences or expected age-referred level is crucial for the diagnosis of any cognitive syndrome. In an ideal context, premorbid cognitive evaluation will allow clinicians to compare current and further evaluations to determine if a rate of significant decline is present. However, in most cases, cognitive assessment is done once some degree of subjective cognitive complains are indicated by the patient. Thus, no clear premorbid cognitive status uses to be available. Estimating premorbid IQ represents a standardized approach to address this question that can be done using instruments such the Wechsler Test of Adult Reading or the National Adult Reading Test. Accordingly, current cognitive status can be then compared to premorbid IQ. The follow-up routine along these time points where minimum clinical change is expected to be significantly measured represents a core method [64].

Tests results falling between −1 and −2 SD from the expected or premorbid level can be considered as characteristic of MCI, while larger deviations of more than −2 SD are more typical for patients who crossed the threshold of dementia. As mentioned before, the construct of PD-MCI is still waiting for a validation consensus, and their diagnostic criteria have been recently defined in consensus by the MDS task force on PD-MCI to avoid potential confusion arising from different definitions that may hamper targeted intervention. These criteria require validation with further research using comprehensive neuropsychological assessment and comparison with commonly used standardized rating scales. When using ad hoc comprehensive neuropsychological batteries for research, the definition of PD-MCI can be based on patient's performance in different cognitive domains (including attention, execution, memory, visuospatial, and language). For each cognitive domain, averaged z scores of tests included in that domain can be calculated and compared with normalized data for each test or using a control group of healthy subjects without dementia and performing multiple regression analysis adjusting for age, education, and sex. Using this method, PD patients can be diagnosed with PD-MCI when the difference between the actual cognitive domain z score and the expected z score is below −1.5 or 2 on at least one out of the five cognitive domains. It is not recommendable using more than two tests for domain to avoid increasing the probabilities of statistical bias towards overdiagnosing cognitive impairment.

Tools for Functional Assessment in PD

Functional assessment results crucial in front of the need to delimitate the cognitive status of the patient [67]. Given the course of PD-MCI, functional assessment should be done to delineate whether or not cognitive alterations have an impact over

IADL. Functional assessment instruments should be selected based on the avoidance of confounders such as motor impairment.

The Parkinson's Disease: Cognitive Functional Rating Scale (PD-CFRS)

The PD-CFRS was developed based on the lack of specific instruments of functional assessment controlling for motor aspects. The PD-CFRS is a brief questionnaire addressed to explore a wide range of functional aspects suspected to be sensible to CI in PD, minimizing the motor impact of the disease. The scale is administered to a knowledgeable informant in an interview form by 12 items selected to cover the spectrum of instrumental cognitive changes seen in PD over the last 2 weeks before the evaluation. Cutoff score ≥3 points demonstrated good clinimetric properties (sensitivity: 0.84; NPV: 0.83) recognizing patients presenting PD-MCI and some degree of functional impairment. Moreover, an increase of 2 points after 6-month follow-up was associated with a clinically significant worsening of the cognitive functional status.

The Brief Penn Daily Activities Questionnaire (PDAQ)

The PDAQ is a 15-item functional scale focused on specific issues regarding cognitive impairment in PD. Preliminary results showed that the PDAQ presents good discriminant validity across stages of cognitive impairment in PD and correlates highly with global cognitive performance.

Management of Cognitive Impairment in PD

Effects of Dopaminergic Stimulation on Cognition

Mild cognitive impairment in PD is mainly characterized by dopaminergic-related dysfunctions, such as defects in verbal fluencies, working-memory, sustained attention, visuospatial disturbances, and free-recall verbal memory. As stated before, in the early to mid PD stages, in which patients still have a stable motor response to dopaminergic agents, several studies have demonstrated an improvement of all these domains, either on dopamine agonists or levodopa, that is maintained 12–18 months after treatment onset. Compared to levodopa, pramipexole exhibited lower benefits in verbal fluency and Luria's palm-edge-fist test [39]. Recently, in a double-blind, placebo-controlled, multicenter study, patients receiving rasagiline, a selective monoamine oxidase type-B inhibitor that enhances central dopaminergic transmission, attentional and executive tasks improved, with no changes in other cognitive domains [81].

All these benefits, however, are not usually sufficient so as to compensate for all deficits, and tend to deteriorate at 18–24 months of follow-up, despite optimal control of motor parkinsonian signs. In advanced patients with motor complications, levodopa may even induce impairment in frontal-executive tasks (i.e., Wisconsin card sorting test) 1–4 h after each levodopa dose [37, 39].

As a whole, it seems that dopaminergic replacement does not recover cognition efficiently and has a limited effect in time, with very modest or even transient deleterious effects on cognition from mid to advanced stages of the disease [39, 40, 82].

Effects of Cholinergic Stimulation on Cognition

Despite the long-standing evidence supporting the role of cholinergic deficits for the development and progression of cognitive deterioration in PD, few studies have accomplished to demonstrate a benefit in cognition through cholinergic stimulation.

Initial open-label studies with different cholinesterase inhibitors (donepezil, rivastigmine, galantamine) observed significant improvement in attention, memory, and visuoperceptive tasks in PDD. Regarding PD-MCI, there is a lack of clinical trials focusing on the potential therapeutic and/or neuroprotective effects that cholinergic stimulation should exert on transition to PDD.

Conclusion

Cognitive impairment is a key feature of PD that can be recognized in most of the patients from the earliest stages and at any time along the course of the disease [2]. Cognitive impairment has important clinical implications since it can indicate an aggregated risk for further development of dementia [7, 12, 25]. However, dissimilarly than the observed in the field of AD, in PD the presence of cognitive alterations that can be labeled, MCI does not always indicate progression to dementia in a short period of time [14, 26].

In PD, different cognitive profiles have been linked to major or minor risk for developing dementia [13, 16, 26, 27]. Thus, common frontal-subcortical cognitive alterations seen in most of the patients and mainly attributable to the concurrent dopaminergic deficiency can result in a relatively benign course remaining stable a long time [26]. In contrast, with independence on the degree of frontal-subcortical alterations, the addition of AD-like or more posterior cortical defects appears to herald higher risk for developing dementia.

PD-MCI can be characterized as the presence of a sum of measurable cognitive alterations fulfilling with the standards proposed by the MDS [50]. These alterations can affect single or multiple domains despite that the more common early findings

are alteration on executive functions. While dysexecutive alterations may follow a linear pattern of decline, cortical alterations can appear at any time along the course of the disease added to frontal-subcortical alterations. These posterior cortical alterations seem to define a more aggressive pattern of cognitive impairment [26, 27]. Thus, cognitive assessment in PD must be done focusing on the whole spectrum of PD-associated cognitive impairment. As there is considerable heterogeneity within PD-MCI, further stratification of different subtypes may be necessary when selecting patients for clinical trials if certain subtypes or cognitive domains are shown to be more relevant than others for predicting dementia. To properly characterize PD-MCI, accurate neuropsychological assessment is needed. Different tools have been tested in the field of cognitive assessment in PD. However, a first approach should be done through screening methods [25].

Mild cognitive impairment can have some degree of impact over ADL [67]. Based on the interference that motor alteration should exert over IADL, the impact of cognition over functionality should be addressed through specific instruments that control for this confounding variable [67].

References

1. Janvin C, Aarsland D, Larsen JP, Hugdahl K. Neuropsychological profile of patients with Parkinson's disease without dementia. Dement Geriatr Cogn Disord. 2003;15(3):126–31. Epub 2003/02/14.
2. Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology. 2005;65(8):1239–45. Epub 2005/10/26.
3. Caviness JN, Driver-Dunckley E, Connor DJ, Sabbagh MN, Hentz JG, Noble B, et al. Defining mild cognitive impairment in Parkinson's disease. Mov Disord. 2007;22(9):1272–7. Epub 2007/04/07.
4. Aarsland D, Bronnick K, Williams-Gray C, Weintraub D, Marder K, Kulisevsky J, et al. Mild cognitive impairment in Parkinson disease: a multicenter pooled analysis. Neurology. 2010;75(12):1062–9. Epub 2010/09/22.
5. Aarsland D, Kurz MW. The epidemiology of dementia associated with Parkinson's disease. Brain Pathol. 2010;20(3):633–9. Epub 2010/06/05.
6. Aarsland D, Muniz G, Matthews F. Nonlinear decline of mini-mental state examination in Parkinson's disease. Mov Disord. 2011;26(2):334–7. Epub 2010/10/21.
7. Buter TC, van den Hout A, Matthews FE, Larsen JP, Brayne C, Aarsland D. Dementia and survival in Parkinson disease: a 12-year population study. Neurology. 2008;70(13):1017–22. Epub 2008/03/26.
8. Clarimon J, Kulisevsky J. Parkinson's disease: from genetics to clinical practice. Curr Genomics. 2013;14(8):560–7. Epub 2014/02/18.
9. Committee GPsDSS. Factors impacting on quality of life in Parkinson's disease: results from an international survey. Mov Disord. 2002;17(1):60–7. Epub 2002/02/09.
10. Aarsland D, Bronnick K, Ehrt U, De Deyn PP, Tekin S, Emre M, et al. Neuropsychiatric symptoms in patients with Parkinson's disease and dementia: frequency, profile and associated care giver stress. J Neurol Neurosurg Psychiatry. 2007;78(1):36–42. Epub 2006/07/06.
11. Muslimovic D, Post B, Speelman JD, Schmand B, de Haan RJ. Determinants of disability and quality of life in mild to moderate Parkinson disease. Neurology. 2008;70(23):2241–7. Epub 2008/06/04.

12. Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sorensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol. 2003;60(3):387–92. Epub 2003/03/14.
13. Janvin CC, Larsen JP, Aarsland D, Hugdahl K. Subtypes of mild cognitive impairment in Parkinson's disease: progression to dementia. Mov Disord. 2006;21(9):1343–9. Epub 2006/05/25.
14. Williams-Gray CH, Foltynie T, Brayne CE, Robbins TW, Barker RA. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain. 2007;130(Pt 7):1787–98. Epub 2007/05/31.
15. Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol. 1999;56(3):303–8. Epub 1999/04/06.
16. Martinez-Horta S, Kulisevsky J. Is all cognitive impairment in Parkinson's disease "mild cognitive impairment"? J Neural Transm. 2011;118(8):1185–90. Epub 2011/06/23.
17. Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord. 2008;23(6):837–44. Epub 2008/03/01.
18. Aarsland D, Bronnick K, Larsen JP, Tysnes OB, Alves G. Cognitive impairment in incident, untreated Parkinson disease: the Norwegian ParkWest study. Neurology. 2009;72(13):1121–6. Epub 2008/11/21.
19. Pagonabarraga J, Corcuera-Solano I, Vives-Gilabert Y, Llebaria G, Garcia-Sanchez C, Pascual-Sedano B, et al. Pattern of regional cortical thinning associated with cognitive deterioration in Parkinson's disease. PLoS One. 2013;8(1):e54980. Epub 2013/01/30.
20. Martinez-Horta S, Pagonabarraga J, Fernandez de Bobadilla R, Garcia-Sanchez C, Kulisevsky J. Apathy in Parkinson's disease: more than just executive dysfunction. J Int Neuropsychol Soc. 2013;19(5):571–82. Epub 2013/02/22.
21. Pagonabarraga J, Kulisevsky J. Cognitive impairment and dementia in Parkinson's disease. Neurobiol Dis. 2012;46(3):590–6. Epub 2012/04/10.
22. Nandhagopal R, Kuramoto L, Schulzer M, Mak E, Cragg J, McKenzie J, et al. Longitudinal evolution of compensatory changes in striatal dopamine processing in Parkinson's disease. Brain. 2011;134(Pt 11):3290–8. Epub 2011/11/15.
23. Pillon B, Dubois B, Cusimano G, Bonnet AM, Lhermitte F, Agid Y. Does cognitive impairment in Parkinson's disease result from non-dopaminergic lesions? J Neurol Neurosurg Psychiatry. 1989;52(2):201–6. Epub 1989/02/01.
24. Monchi O, Petrides M, Doyon J, Postuma RB, Worsley K, Dagher A. Neural bases of set-shifting deficits in Parkinson's disease. J Neurosci. 2004;24(3):702–10. Epub 2004/01/23.
25. Kulisevsky J, Pagonabarraga J. Cognitive impairment in Parkinson's disease: tools for diagnosis and assessment. Mov Disord. 2009;24(8):1103–10. Epub 2009/04/09.
26. Williams-Gray CH, Evans JR, Goris A, Foltynie T, Ban M, Robbins TW, et al. The distinct cognitive syndromes of Parkinson's disease: 5 year follow-up of the CamPaIGN cohort. Brain. 2009;132(Pt 11):2958–69. Epub 2009/10/09.
27. Pagonabarraga J, Kulisevsky J, Llebaria G, Garcia-Sanchez C, Pascual-Sedano B, Gironell A. Parkinson's disease-cognitive rating scale: a new cognitive scale specific for Parkinson's disease. Mov Disord. 2008;23(7):998–1005. Epub 2008/04/03.
28. Scatton B, Rouquier L, Javoy-Agid F, Agid Y. Dopamine deficiency in the cerebral cortex in Parkinson disease. Neurology. 1982;32(9):1039–40. Epub 1982/09/01.
29. Halliday GM, McCann H. The progression of pathology in Parkinson's disease. Ann N Y Acad Sci. 2010;1184:188–95. Epub 2010/02/12.
30. Yeterian EH, Pandya DN. Prefrontostriatal connections in relation to cortical architectonic organization in rhesus monkeys. J Comp Neurol. 1991;312(1):43–67. Epub 1991/10/01.
31. Yeterian EH, Pandya DN. Corticothalamic connections of the superior temporal sulcus in rhesus monkeys. Exp Brain Res. 1991;83(2):268–84. Epub 1991/01/01.
32. Pagonabarraga J, Soriano-Mas C, Llebaria G, Lopez-Sola M, Pujol J, Kulisevsky J. Neural correlates of minor hallucinations in non-demented patients with Parkinson's disease. Parkinsonism Relat Disord. 2014;20(3):290–6. Epub 2014/01/01.

33. Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res. 2004;318(1):121–34. Epub 2004/09/01.
34. MacDonald AA, Monchi O, Seergobin KN, Ganjavi H, Tamjeedi R, MacDonald PA. Parkinson's disease duration determines effect of dopaminergic therapy on ventral striatum function. Mov Disord. 2013;28(2):153–60. Epub 2012/11/21.
35. Gotham AM, Brown RG, Marsden CD. 'Frontal' cognitive function in patients with Parkinson's disease 'on' and 'off' levodopa. Brain. 1988;111(Pt 2):299–321. Epub 1988/04/01.
36. Monchi O, Petrides M, Mejia-Constain B, Strafella AP. Cortical activity in Parkinson's disease during executive processing depends on striatal involvement. Brain. 2007;130(Pt 1):233–44. Epub 2006/11/24.
37. Kulisevsky J. Role of dopamine in learning and memory: implications for the treatment of cognitive dysfunction in patients with Parkinson's disease. Drugs Aging. 2000;16(5):365–79. Epub 2000/08/05.
38. Kulisevsky J, Avila A, Barbanoj M, Antonijoan R, Berthier ML, Gironell A. Acute effects of levodopa on neuropsychological performance in stable and fluctuating Parkinson's disease patients at different levodopa plasma levels. Brain. 1996;119(Pt 6):2121–32. Epub 1996/12/01.
39. Kulisevsky J, Garcia-Sanchez C, Berthier ML, Barbanoj M, Pascual-Sedano B, Gironell A, et al. Chronic effects of dopaminergic replacement on cognitive function in Parkinson's disease: a 2-year follow-up study of previously untreated patients. Mov Disord. 2000;15(4):613–26. Epub 2000/08/06.
40. Cools R, Stefanova E, Barker RA, Robbins TW, Owen AM. Dopaminergic modulation of high-level cognition in Parkinson's disease: the role of the prefrontal cortex revealed by PET. Brain. 2002;125(Pt 3):584–94. Epub 2002/03/02.
41. Cools R, Lewis SJ, Clark L, Barker RA, Robbins TW. L-DOPA disrupts activity in the nucleus accumbens during reversal learning in Parkinson's disease. Neuropsychopharmacology. 2007;32(1):180–9. Epub 2006/07/15.
42. Kehagia AA, Barker RA, Robbins TW. Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. Lancet Neurol. 2010;9(12):1200–13. Epub 2010/10/01.
43. Nakano I, Hirano A. Parkinson's disease: neuron loss in the nucleus basalis without concomitant Alzheimer's disease. Ann Neurol. 1984;15(5):415–8. Epub 1984/05/01.
44. Dubois B, Pilon B, Lhermitte F, Agid Y. Cholinergic deficiency and frontal dysfunction in Parkinson's disease. Ann Neurol. 1990;28(2):117–21. Epub 1990/08/01.
45. Pillon B, Dubois B, Bonnet AM, Esteguy M, Guimaraes J, Vigouret JM, et al. Cognitive slowing in Parkinson's disease fails to respond to levodopa treatment: the 15-objects test. Neurology. 1989;39(6):762–8. Epub 1989/06/01.
46. Shimada H, Hirano S, Shinotoh H, Aotsuka A, Sato K, Tanaka N, et al. Mapping of brain acetylcholinesterase alterations in Lewy body disease by PET. Neurology. 2009;73(4):273–8. Epub 2009/05/29.
47. Galvin JE. Cognitive change in Parkinson disease. Alzheimer Dis Assoc Disord. 2006;20(4):302–10. Epub 2006/11/30.
48. Klein JC, Eggers C, Kalbe E, Weisenbach S, Hohmann C, Vollmar S, et al. Neurotransmitter changes in dementia with Lewy bodies and Parkinson disease dementia in vivo. Neurology. 2010;74(11):885–92. Epub 2010/02/26.
49. Hilker R, Thomas AV, Klein JC, Weisenbach S, Kalbe E, Burghaus L, et al. Dementia in Parkinson disease: functional imaging of cholinergic and dopaminergic pathways. Neurology. 2005;65(11):1716–22. Epub 2005/12/14.
50. Litvan I, Goldman JG, Troster AI, Schmand BA, Weintraub D, Petersen RC, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: movement disorder society task force guidelines. Mov Disord. 2012;27(3):349–56. Epub 2012/01/26.
51. Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, et al. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord. 2007;22(12):1689–707; quiz 837; Epub 2007/06/02.
52. Jellinger KA. Neurobiology of cognitive impairment in Parkinson's disease. Expert Rev Neurother. 2012;12(12):1451–66. Epub 2012/12/15.

53. Seto-Salvia N, Clarimon J, Pagonabarraga J, Pascual-Sedano B, Campolongo A, Combarros O, et al. Dementia risk in Parkinson disease: disentangling the role of MAPT haplotypes. Arch Neurol. 2011;68(3):359–64. Epub 2011/03/16.
54. Seto-Salvia N, Pagonabarraga J, Houlden H, Pascual-Sedano B, Dols-Icardo O, Tucci A, et al. Glucocerebrosidase mutations confer a greater risk of dementia during Parkinson's disease course. Mov Disord. 2012;27(3):393–9. Epub 2011/12/17.
55. Petersen RC. Mild cognitive impairment as a diagnostic entity. J Intern Med. 2004;256(3):183–94. Epub 2004/08/25.
56. Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, et al. Current concepts in mild cognitive impairment. Arch Neurol. 2001;58(12):1985–92. Epub 2001/12/26.
57. Litvan I, Aarsland D, Adler CH, Goldman JG, Kulisevsky J, Mollenhauer B, et al. MDS Task Force on mild cognitive impairment in Parkinson's disease: critical review of PD-MCI. Mov Disord. 2011;26(10):1814–24. Epub 2011/06/11.
58. Dubois B. Is PD-MCI a useful concept? Mov Disord. 2007;22(9):1215–6. Epub 2007/06/09.
59. Goldman JG, Weis H, Stebbins G, Bernard B, Goetz CG. Clinical differences among mild cognitive impairment subtypes in Parkinson's disease. Mov Disord. 2012;27(9):1129–36. Epub 2012/07/11.
60. Yu RL, Wu RM, Tai CH, Lin CH, Cheng TW, Hua MS. Neuropsychological profile in patients with early stage of Parkinson's disease in Taiwan. Parkinsonism Relat Disord. 2012;18(10):1067–72. Epub 2012/07/04.
61. Foltynie T, Brayne CE, Robbins TW, Barker RA. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain. 2004;127(Pt 3):550–60. Epub 2003/12/24.
62. Villa-Bonomo C, Pagonabarraga J, Martinez-Horta S, Fernandez de Bobadilla R, Garcia-Sanchez C, Campolongo A, et al. Short-lasting episodes of prosopagnosia in Parkinson's disease. Parkinsonism Relat Disord. 2013;19(3):375–7. Epub 2012/12/15.
63. Hosokai Y, Nishio Y, Hirayama K, Takeda A, Ishioka T, Sawada Y, et al. Distinct patterns of regional cerebral glucose metabolism in Parkinson's disease with and without mild cognitive impairment. Mov Disord. 2009;24(6):854–62. Epub 2009/02/10.
64. Marras C, Troster AI, Kulisevsky J, Stebbins GT. The tools of the trade: a state of the art "How to Assess Cognition" in the patient with Parkinson's disease. Mov Disord. 2014;29(5):584–96. Epub 2014/04/24.
65. Troster AI. A precis of recent advances in the neuropsychology of mild cognitive impairment(s) in Parkinson's Disease and a proposal of preliminary research criteria. J Int Neuropsychol Soc. 2011;3:393–406. Epub 2011/04/09.
66. Dubois B, Burn D, Goetz C, Aarsland D, Brown RG, Broe GA, et al. Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society task force. Mov Disord. 2007;22(16):2314–24. Epub 2007/12/22.
67. Kulisevsky J, Fernandez de Bobadilla R, Pagonabarraga J, Martinez-Horta S, Campolongo A, Garcia-Sanchez C, et al. Measuring functional impact of cognitive impairment: validation of the Parkinson's disease cognitive functional rating scale. Parkinsonism Relat Disord. 2013;19(9):812–7. Epub 2013/06/19.
68. Marti MJ, Kulisevsky J. Candidate patient for treatment with continuous apomorphine infusion. Rev Neurol. 2012;55 Suppl 1:S15–9. Epub 2012/10/20. Paciente candidato a tratamiento con apomorfina en infusion continua.
69. Fernandez de Bobadilla R, Pagonabarraga J, Martinez-Horta S, Pascual-Sedano B, Campolongo A, Kulisevsky J. Parkinson's disease-cognitive rating scale: psychometrics for mild cognitive impairment. Mov Disord. 2013;28(10):1376–83. Epub 2013/07/23.
70. Kasten M, Bruggemann N, Schmidt A, Klein C. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. Neurology. 2010;75(5):478; author reply -9. Epub 2010/08/04.
71. Hoops S, Nazem S, Siderowf AD, Duda JE, Xie SX, Stern MB, et al. Validity of the MoCA and MMSE in the detection of MCI and dementia in Parkinson disease. Neurology. 2009;73(21):1738–45. Epub 2009/11/26.

72. Dalrymple-Alford JC, MacAskill MR, Nakas CT, Livingston L, Graham C, Crucian GP, et al. The MoCA: well-suited screen for cognitive impairment in Parkinson disease. Neurology. 2010;75(19):1717–25. Epub 2010/11/10.
73. Isella V, Mapelli C, Morielli N, De Gaspari D, Siri C, Pezzoli G, et al. Validity and metric of MiniMental Parkinson and MiniMental State Examination in Parkinson's disease. Neurol Sci. 2013;34(10):1751–8. Epub 2013/02/21.
74. Volkmann J, Albanese A, Antonini A, Chaudhuri KR, Clarke CE, de Bie RM, et al. Selecting deep brain stimulation or infusion therapies in advanced Parkinson's disease: an evidence-based review. J Neurol. 2013;260(11):2701–14. Epub 2013/01/05.
75. Berardelli A, Wenning GK, Antonini A, Berg D, Bloem BR, Bonifati V, et al. EFNS/MDS-ES/ENS [corrected] recommendations for the diagnosis of Parkinson's disease. Eur J Neurol. 2013;20(1):16–34. Epub 2013/01/03.
76. Llebaria G, Pagonabarraga J, Kulisevsky J, Garcia-Sanchez C, Pascual-Sedano B, Gironell A, et al. Cut-off score of the Mattis Dementia Rating Scale for screening dementia in Parkinson's disease. Mov Disord. 2008;23(11):1546–50. Epub 2008/06/12.
77. Pirogovsky E, Schiehser DM, Litvan I, Obtera KM, Burke MM, Lessig SL, et al. The utility of the Mattis Dementia Rating Scale in Parkinson's disease mild cognitive impairment. Parkinsonism Relat Disord. 2014;20(6):627–31. Epub 2014/04/09.
78. Moro E, Lozano AM, Pollak P, Agid Y, Rehncrona S, Volkmann J, et al. Long-term results of a multicenter study on subthalamic and pallidal stimulation in Parkinson's disease. Mov Disord. 2010;25(5):578–86. Epub 2010/03/10.
79. Davila G, Berthier ML, Kulisevsky J, Asenjo B, Gomez J, Lara JP, et al. Structural abnormalities in the substantia nigra and neighbouring nuclei in Tourette's syndrome. J Neural Transm. 2010;117(4):481–8. Epub 2010/02/05.
80. Kulisevsky J, Pagonabarraga J. Tolerability and safety of ropinirole versus other dopamine agonists and levodopa in the treatment of Parkinson's disease: meta-analysis of randomized controlled trials. Drug Saf. 2010;33(2):147–61. Epub 2010/01/20.
81. Emre M, Poewe W, De Deyn PP, Barone P, Kulisevsky J, Pourcher E, et al. Long-term safety of rivastigmine in parkinson disease dementia: an open-label, randomized study. Clin Neuropharmacol. 2014;37(1):9–16. Epub 2014/01/18.
82. Cooper JA, Sagar HJ, Doherty SM, Jordan N, Tidswell P, Sullivan EV. Different effects of dopaminergic and anticholinergic therapies on cognitive and motor function in Parkinson's disease. A follow-up study of untreated patients. Brain. 1992;115(Pt 6):1701–25. Epub 1992/12/01.