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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

# Mild cognitive impairment in Parkinson's disease

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**Abstract**
Understanding on the clinical features and neural mechanisms leading to cognitive impairment and dementia in Parkinson's disease (PD) has notably increased. At time of diagnosis, nearly all PD patients present some degree of cognitive impairment not enough severe as to significantly affect functional independence. However, even mild cognitive changes have a measurable impact to functional capacity in PD. A clinically practical differentiation is based on the importance of executive deficits in the early phases of cognitive impairment in PD and on the evidence stressing the transitional role of posterior–cortical impairment on the progression of PD-MCI to dementia. However, the pattern of cognitive impairment in PD is variable not just to the extents on which are the affected cognitive domains, but also on which are those domains that became affected first. Specific diagnostic criteria for mild cognitive impairment associated with PD (PD-MCI) and dementia (PDD) and operative guidelines for the cognitive assessment have been developed. In the present review, we will describe general notions regarding the mechanisms and the profile of cognitive deterioration in PD, the diagnostic criteria for PD-MCI, and some of the currently recommended assessment approaches.

**Keywords** Parkinson's disease · PD-MCI · Cognitive assessment

## Introduction

Parkinson's disease (PD) was initially defined as a pure motor disease clinically characterized by the presence of four cardinal clinical features: Bradykinesia, resting tremor, rigidity, and postural instability. However, compelling evidence demonstrated that different non-motor features are inseparable from PD (Obeso et al. 2017; Postuma et al. 2015). Among them, cognitive impairment of different severity and the eventual progression to dementia is known to be a common complication appearing at some point along the course of the disease in a large proportion of PD patients (Aarsland et al. 2010). The high frequency and devastating impact of cognitive deficits in PD has increasingly been recognized in recent years (Obeso et al. 2017). However, the mechanisms leading to cognitive impairment and dementia in PD are only partially understood and there is a lack of effective therapeutic strategies aimed to mitigate or delay cognitive deterioration in PD.

Knowledge on the clinical features and neural mechanisms leading to cognitive impairment and dementia in PD has notably increased in the past 15 years (Barone et al. 2011). More recently, specific diagnostic criteria for mild cognitive deficits associated with PD (PD-MCI) and dementia (PDD) and operative guidelines for the cognitive assessment have been developed. In the present review, we will describe general notions regarding the mechanisms and the profile of cognitive deterioration in PD, the diagnostic criteria for PD-MCI, and some of the currently recommended assessment approaches (Kulisevsky and Pagonabarraga 2009).

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## Neuropsychological aspects of Parkinson's disease

Cognitive impairment, and specifically dementia associated with PD, was formally considered a late complication of the disease (Aarsland et al. 2001; Hely et al. 2008). However, compelling evidence proved that cognitive impairment of variable severity can occur in the early stages of the disease (Kulisevsky et al. 2000; Postuma et al. 2015). At time of diagnosis, nearly all PD patients present some degree of cognitive impairment not enough sever as to significantly affect functional independence (Muslimovic et al. 2005; Postuma et al. 2015). However, mild cognitive changes have a measurable impact to functional capacity in PD (Kulisevsky et al. 2013). These early signs of cognitive deterioration are, in many cases, difficult to capture with common screening methods (Aarsland et al. 2009; Muslimovic et al. 2005). It highlights that early mild cognitive deficits associated with PD are, in many cases, not clinically apparent, so formal neuropsychological examination is required (Kulisevsky and Pagonabarraga 2009).

The prototypical neuropsychological pattern of cognitive impairment in PD is predominantly characterized by frontal–executive deficits resembling those observed in patients with prefrontal cortex (PFC) damage (Williams-Gray et al. 2009a). That is, slowed processing speed, attention and working memory, set-shifting, planning, and non-cued facilitated recall often characterize the profile of cognitive impairment in PD (Barone et al. 2011). These difficulties are mostly attributed to the dopamine-mediated dysfunction of the associative circuit of the basal ganglia which maintains reciprocal connections between the dorsal caudate nucleus and the dorsal–lateral prefrontal cortex (DLPFC) (Carbon et al. 2004). On the other hand, some deficits frequently observed in PD patients under dopaminergic replacement and affecting tasks involving the ventro-medial and the orbital PFC are assumed to be a consequence of an excessive dopaminergic stimulation over circuits remaining relatively spared (Cools et al. 2002; Kulisevsky et al. 1996).

In any case, despite frontal–executive difficulties appear as the more characteristically affected cognitive domain in early PD, up to 40% of patients also exhibit deficits in other cognitive domains like visuospatial skills, memory, or language (Muslimovic et al. 2005). In fact, the pattern of cognitive impairment in PD is variable not just to the extents on which are the affected cognitive domains, but also on which are those domains that became affected first.

In terms of progression, despite the occurrence of dementia is not inevitable in all cases, it affects up to 36% of patients after 4 years of follow-up and up to 80% of long-term survival patients above 20 years of disease progression. It means that PD imposes a risk for developing dementia six times greater than the observed in general population (Aarsland et al. 2003, 2005, 2010; Hely et al. 2008).

From the field of AD, we have learnt that early cognitive deficits not severe enough as to significantly impact functionality (mild cognitive impairment or MCI) define a transitional stage between normal cognition and dementia (Petersen et al. 1999). In PD, however, the profile and pattern of progression of PD-MCI is quite heterogeneous between individuals (Mihaescu et al. 2018). Despite it is undeniable that the presence of PD-MCI is strongly associated with an increased risk for the development of dementia, not all patients exhibit the same cognitive profile or the same rate of progression (Aarsland et al. 2004). Longitudinal studies indicate that the presence of deficits in cognitive domains extending beyond executive functions, and involving cortical–instrumental abilities, is more predictable of progression to dementia in PD (Pagonabarraga et al. 2008; Williams-Gray et al. 2009a). This is especially notable in patients exhibiting impaired language and semantic verbal fluency and defective visuospatial/visuoconstructive abilities. It suggests that specific profiles of PD-MCI could associate a different risk and rate of progression to dementia (Martinez-Horta and Kulisevsky 2011). However, the mechanisms subserving the relative preservation of cognitive status in some cases or its progression to dementia in others are not fully understood.

From a neuropsychological perspective, multiple studies showed that difficulties in visuoperceptive and visuoconstructive tasks, language, and episodic memory characterize the cognitive profile of PDD (Emre et al. 2007). Paralleling the progression of cognitive deterioration, neuroimaging studies, illustrated that posterior–cortical cholinergic presynaptic deficits in primary and associative occipital, parietal, and temporal areas increase over the course of PD (Hilker et al. 2005). More recent data also suggest the involvement of dopaminergic denervation on posterior–cortical thinning (Sampedro et al. 2018a). Neuropathological studies performed in patients who developed PDD showed the involvement of widespread cortical and limbic neurodegeneration, and deposition of Lewy bodies and Lewy neurites (Halliday et al. 2014). Co-existing amyloid pathology, cerebrovascular disease, and multiple neurotransmitter system dysfunction are also present in PDD (Hepp et al. 2016; Johar et al. 2017; Vesely and Rektor 2016). It suggests that multiple mechanisms could mediate synergistic processes leading to more aggressive forms of cognitive deteriorations.

Older age, disease duration, worst motor function, comorbid neuropsychiatric features, and worst cognitive performance at baseline are variables associated with increased prevalence of PDD (Emre et al. 2007; Litvan et al. 2011). As said, the

mechanisms leading to a worst prognosis in terms of cognitive progression in PD are partially understood, but seem undisputable that the variable expression of the disease also responds to genetic and to environmental mechanisms.

Environmental factors such as social enrichment are known to contribute to better cognitive status in older general population. In PD, social interactions can be limited due to the relation of motor symptoms and/or neuropsychiatric features with social isolation. However, even when proper social participation is present, the variability in cognitive progression still existing. Obesity, hypertension, and other comorbidities such as diabetes also account for a worst cognitive outcome (Smith et al. 2011; van den Berg et al. 2009; Wang et al. 2016).

Some genetic causes of PD like the LRRK2 are not associated with dementia. Conversely, GBA and MAPT mutations are known to contribute to more rapid progression with severe mild cognitive deficits and dementia in PD (Goris et al. 2007; Mata et al. 2014; Morley et al. 2012; Sampedro et al. 2018b; Seto-Salvia et al. 2011). The ApoE4 allele was shown to contribute to amnestic and semantic verbal memory deficits, which, as said, are associated with a cognitive profile of more risk for the development of dementia (Mata et al. 2014; Morley et al. 2012; Williams-Gray et al. 2009b). The role of polymorphism in other genes like the BDNF or the COMT is still conflicting (Guerini et al. 2009; Irwin et al. 2012; Morley et al. 2012). However, a recent study demonstrated that COMT Val/Val homozygotes have a reduced gray matter volume in fronto-temporo-parietal territories and a more severe pattern of cognitive decline (Sampedro et al. 2019). In any case, there is no debate on the multifactorial origin of a cascade of processes that leads to more severe cognitive deterioration in some patients affected by PD.

Neuroimaging data support that posterior–cortical brain changes are characteristically associated with the increased risk for the development of dementia. Accordingly, the addition of posterior–cortical-type deficits in association with widespread cortico-subcortical synuclein pathology and cholinergic changes seems to better characterize the progression of cognitive impairment to PDD than the inherent executive dysfunction present in most patients (Halliday et al. 2014; Williams-Gray et al. 2009a). This notion stressed the idea about defining methods to properly capture cognitive phenotypes of variable risk of cognitive progression to dementia.

## The operative definition and assessment of Parkinson's disease mild cognitive impairment (PD-MCI)

The MDS (Movement Disorder Society) Task Force on MCI in PD has established an operative definition of PD-MCI to homogenize clinical practice and research (Litvan et al. 2011). This task force determined the diagnostic criteria of PD-MCI and the instruments and procedures recommended to properly capture the presence of these criteria (Marras et al. 2014; Skorvanek et al. 2018).

Accordingly, the formal diagnosis of PD-MCI is based on the accomplishment of four key features in the absence of exclusion criteria (see Table 1). This includes evidence of a gradual cognitive decline reported by the patient, relative, or clinician that is objectivized through Level I or Level II testing, and that is not enough severe as to significantly interfere functional independence. Level I testing is based on PD-validated scales of global cognitive performance. Level II testing is based on comprehensive neuropsychological assessment. This latter must be done exploring five cognitive domains (attention, executive function, memory, visuospatial functions, and language) using two single tests for each domain. Using Level I testing, PD-MCI is diagnosed on the basis of either impaired performance on a global cognitive scale validated for being used in PD, or impairment in at least two tests when a limited neuropsychological assessment battery (less than two tests in the five domains) is administered. Level I testing can be assumed as a practical but limited approach to PD-MCI diagnosis, since this method does not allow subtyping patients in different PD-MCI profiles. Using Level II testing, PD-MCI is diagnosed when impairment is captured on at least two tests represented by either two tests in the same cognitive domain, or one test in two different cognitive domains. Thus, impairment must be demonstrated by means of a performance 1.5 SD below normative data or a significant cognitive decline on serial cognitive testing, or a significant decline from estimated premorbid level. Although 1 and 2 SD below normative data have also been used, most authors agree that 1.5 should be recommended. In any case, the formal diagnosis of PD-MCI through Level I or Level II testing requires the use of standardized and validated methods of cognitive testing in PD (Litvan et al. 2011, 2012).

### Level I cognitive assessment

Level I assessment consists on abbreviated methods of cognitive assessment through the use of PD-validated global cognitive assessment instruments. Another approach is the use of brief neuropsychological batteries assessing each cognitive domain with one test or not assessing all cognitive domains. It is the case, for example, of batteries focusing on memory and executive functions but not on language or visuospatial skills (Table 2).

Up to date, multiple global cognitive assessment instruments have been used to assess cognition in PD. Some of them were not specifically developed to be used in PD despite they were subjected to validation studies (i.e., MMSE or MoCA) (Kulisevsky and Pagonabarraga 2009;

**Table 1** MDS Task force criteria for PD-MCI

| |
|---|
| I. Inclusion criteria |
| Diagnosis of Parkinson's disease as based on the UK PD Brain Bank Criteria20 |
| Gradual decline, in the context of established PD, in cognitive ability reported by either the patient or informant, or observed by the clinician |
| Cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities (detailed in section III) |
| Cognitive deficits are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present |
| II. 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 |
| III. 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 PDa 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 to 2 SDs below appropriate norms or |
| Significant decline demonstrated on serial cognitive testing or |
| Significant decline from estimated premorbid levels |
| IV. 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) |

**Table 2** Level I instruments for cognitive assessment in PD

| | Cognitive domains | Internal consistency | Test–retest reliability | Inter-rater reliability | Content validity | Construct validity | Acceptability |
|---|---|---|---|---|---|---|---|
| Generic scales | | | | | | | |
| MMSE | Memory, orientation, language | ND | ND | ND | ND | ND | ND |
| MDRS | Fronto-subcortical | | | | | | |
| CAMCOG | Orientation, language, memory, attention, calculation, praxis, perception | ND | ND | ND | ND | ND | ND |
| FAB | Frontal functions | ++ | ++ | ++ | +++ | +++ | |
| PD-specific scales | | | | | | | |
| MMP | Orientation, visual scanning, attention, verbal fluency, visual memory, verbal processing | ND | ND | ND | ++ | +++ | − |
| SCOPA-COG | Memory, attention, executive functions, visuospatial functions | +++ | +++ | ND | + | +++ | + |
| PANDA | Immediate and delayed memory, verbal fluency, visuospatial function, attention, working memory | ND | ND | ND | ++ | +++ | − |
| PD-CRS | Frontal functions/posterior–cortical functions | +++ | ++++ | ++++ | +++ | +++ | + |

Marras et al. 2014). Others like the Parkinson's disease—Cognitive Rating Scale (PD-CRS) or the SCOPA-Cog—are PD-specific cognitive assessment instruments (Kulisevsky and Pagonabarraga 2009). The MDS Rating Scales Review Committee recently assessed the clinimetric properties of 12 of commonly used Level I instruments. Among these 12 scales, three were classified as recommended: The PD-CRS, the Montreal Cognitive Assessment (MoCA), and the Mattis Dementia Rating Scale Second Edition (MDRS-2) (Skorvanek et al. 2018). However, of the three instruments, only the PD-CRS was a PD-specific instrument. Despite the acceptable psychometric properties of the MoCA and the MDRS-2 for the screening of PD-MCI, no one of these two instruments were developed specifically focusing on the characteristics of cognitive impairment in PD. It means that the construct validity of these scales may be good capturing global cognitive changes occurring in general forms of cognitive deterioration like amnestic-type MCI or common frontal–subcortical impairment. However, these instruments may lack on measures sensitive to more specific cognitive changes occurring in PD and specially in the transition to more severe forms of cognitive deterioration in this population (Pagonabarraga et al. 2008).

The PD-CRS was designed to capture the full spectrum of cognitive deficits in PD by separately scoring tasks with a major executive (frontal–subcortical subscore) and posterior–cortical (subscore) dependence, and to provide a global total score (Pagonabarraga et al. 2008). This clinically practical differentiation was based on the importance of executive deficits in the early phases of cognitive impairment in PD and also on the evidence stressing the transitional role of posterior–cortical impairment on the progression of PD-MCI to dementia. The psychometric studies showed that, using a cut-off score of PD-CRS total score < 82, this instrument had a high sensitivity (79%) and specificity (80%) for discriminating the cognitive status between patients with normal cognition and PD-MCI (Fernandez de Bobadilla et al. 2013). Other psychometric attributes of this instrument rely on the time of administration (less than 20 min), test–retest reliability, intra-rater reliability, and responsiveness (Fernandez-Bobadilla et al. 2017; Fernandez de Bobadilla et al. 2013; Pagonabarraga et al. 2008).

Another important aspect makes reference to the obvious impact of mild forms of cognitive impairment over functional independence (Marras et al. 2014). Whereas in the field of Alzheimer's disease, preservation of functional independence is a key feature of amnestic-type MCI, in PD-MCI, it is assumed that, in fact, there is some degree of cognitive-related functional impairment. However, the assessment of functional difficulties related to cognition but not to motor symptoms can be complicated. The Parkinson's Disease—Cognitive Functional Rating Scale (PD-CFRS)—is presently the unique instrument developed and validated to specifically capture the impact of cognitive changes over functionality in PD (Kulisevsky et al. 2013). This instrument consists of 12 items selected to cover the spectrum of instrumental cognitive changes seen in PD. All 12 questions explore with some examples, whether or not the patient has had trouble in performing an activity (0 = none; 1 = some of the time; 2 = most of the time; 8 = the subject has never done the activity in the past) such as handling money, domestic economy, arranging holidays or meetings, handling personal mail, controlling drug treatment schedule, organizing daily activities, handling home electrical appliances, understanding how to use public transport, solving unforeseen events, explaining things he/she want to say, understanding the things he/she read, and handling the cell phone. The maximum score, obtained by the sum of the ratings, is 24.

In the clinimetric study, the PD-CFRS showed intermediate concurrent validity (ICC = 0.50), high test–retest (ICC = 0.82), inter-rater reliability (ICC = 0.80) and internal consistency (Cronbach's $\alpha = 0.79$), and higher coefficient of variation to detect dysfunction in ND-PD patients (PD-CFRS 86.6% vs. OARS-IADL 8.1%). There was a strong relationship between the PD-CFRS and the global cognitive status determined with the PD-Cognitive Rating Scale ($r = -0.72$, $p < 0.0001$). The responsiveness study recruited 63 patients with normal cognition and 57 with mild cognitive impairment (MCI); an increase of two points in the PD-CFRS after 6 months was associated with a clinically significant worsening of the cognitive functional status. According to a discriminant analysis, a PD-CFRS cut-off score of ≥ 3 was found to be optimal for detecting functional impairment in PD-MCI patients (Martinez-Horta and Kulisevsky 2011).

### Level II cognitive assessment

Level II assessment consists on the administration of a comprehensive battery of neuropsychological testing (Goldman et al. 2015). By consensus, the assessment of cognitive status in PD may be addressed over five cognitive domains of interest: Attention and working memory, executive function, language, memory, and visuospatial function. The assessment must be done using at least two tests for each cognitive domain (Goldman et al. 2013; Litvan et al. 2012; Marras et al. 2014). To determine the diagnosis of PD-MCI, impairment must be present on at least two tests, either in the same cognitive domain or in different cognitive domains. The definition of impairment must be determined following common standards on neuropsychological assessment. It is by determining a performance of 1–2 SD below the expected range (Goldman et al. 2013). It implies that the selection of tests to compose a comprehensive neuropsychological assessment battery must be done taking into account the need for the existence of normative data allowing the adjustment for

**Table 3** Neuropsychological tests recommended for Level II assessment

| Cognitive domain | Neuropsychological Tests |
|---|---|
| Attention and working memory | WAIS-IV (or earlier version) Letter Number Sequencing<br>WAIS-IV Coding (or earlier version) or other substitution task, written or oral<br>Trail Making Test<br>Digit span backward or digit ordering<br>Stroop color-word test |
| Executive function | Wisconsin Card Sorting Test (CST), or modified CST (Nelson's modification)<br>Tower of London test–Drexel version, or Stockings of Cambridge (CANTAB)<br>Verbal fluency test, such as letter fluency (COWAT or similar tests), category fluency (animals, supermarket, or similar), or alternating fluency tasks (if a well-standardized version is used). Not more than one verbal fluency test abnormality should be used to satisfy the MCI criterion of two abnormal test performances because of the strong relationship among these tests; ten points Clock Drawing Test |
| Language | WAIS-IV (or earlier version) Similarities<br>Confrontation naming task, such as Boston Naming Test (or short-form validated in PD) or Graded Naming Test |
| Memory | Word list learning test with delayed recall and recognition conditions, such as Rey's Auditory Verbal Learning Test, California Verbal Learning Test, Hopkins Verbal Learning Test, and Selective Reminding Test<br>Prose recall test with a delayed recall condition, such as Wechsler Memory Scale-IV Logical Memory subtest (or earlier version) or Rivermead Behavioral Memory Test paragraph recall subtest<br>Brief Visuospatial Memory Test–Revised (BVMT-R) |
| Visuospatial function | Benton's Judgment of Line Orientation<br>Hooper Visual Organization Test<br>Clock copying (e.g., Royall's CLOX) |

age and education. Other approaches to determine impairment are also determining a pattern of significant decline in consecutive serial testing or a significant decline from estimated premorbid level.

According to the use of two tests for each cognitive domain and the assessment of five cognitive domains, patients can be classified in different subtypes of PD-MCI. This classification may be important both for research and clinical proposes, since it could allow to explore the different neurobiological substrates associated with those subtypes. The presence of two tests impaired in a single cognitive domain with no evidence of impairment in other domains represents a single-domain pattern of PD-MCI. In the case of impairment in at least one test in two or more cognitive domains, it represents a multiple-domain pattern of PD-MCI. More specific sub-classification may be done based on the impaired domains. For instance, in case of prominent alteration of the frontal executive domain with the absence of impairment in other domains, the sub-classification may be PD-MCI single-domain executive type (Barone et al. 2011; Litvan et al. 2011, 2012).

Regarding the list of tests that can be used to compose a reliable comprehensive neuropsychological assessment battery, current recommendations lists multiple instruments for which appropriate sensitivity and specificity of about 81.3% and 85.7% is found using ten specific tests of this list (Goldman et al. 2015). Although there is no mandatory list, a proposal for the recommended instruments for each cognitive domain is:

1. Attention and working memory: Symbol digit modalities test (SDMT) and Trail Making Test part A.
2. Executive functions: Clock drawing test and Trail Making Test part B.
3. Language: Boston Naming Test and Semantic verbal fluency test.
4. Memory: Free and Cued Selective Reminding Test (FCSRT) and Figural memory.
5. Visuospatial function: Judgment of Line Orientation and Copy of pentagons.

Despite these, ten selected tests showed good psychometric properties in the studied sample of reference; there are many other options that could be considered on the basis of, for example, disposition of normative data. Accordingly, the MDS task force listed a set of tests (Table 3) to be considered.

## Conclusion

In PD, cognitive impairment of different severity and profile appears in a vast majority of patients at some point during disease progression and have an enormous impact on health-related quality of life of patients and caregivers (Obeso et al. 2017; Postuma et al. 2015). Despite PD-MCI may be present from the beginning of the disease, it is frequently under recognized in clinical practice (Kulisevsky and Pagonabarraga 2009; Postuma et al. 2015). Subtle signs of cognitive

deterioration may be not captured through unspecific global cognitive assessment methods. However, the progression of mild cognitive deficits to dementia occurs in an extremely important proportion of PD patients. Thus, an operative definition of the diagnostic criteria and the assessment procedures to early capture clinically relevant cognitive changes in PD was an unmet need until few years ago. The diagnostic criteria and recommendations developed within the MDS task force on mild cognitive impairment were done according to FDA requirements, aiming to be used in the context of therapeutic development and also to homogenize how researchers deal with the cognitive classification of PD patients (Litvan et al. 2011, 2012).

Level I and Level II assessment approaches are both validated for the diagnosis of PD-MCI, not all testing methods demonstrated the same construct validity in terms of capturing different cognitive phenotypes. In this context, the PD-CRS appears as a recommended Level I instrument thanks to the sensitivity of this scale differentiating frontal–subcortical to posterior–cortical changes (Goldman et al. 2015; Pagonabarraga et al. 2008). In comprehensive neuropsychological assessment, more specific classifications can be done by covering five cognitive domains with two tests per domain, without excluding those initially considered to be mostly spared in PD (i.e.: episodic memory, language, and visuoconstructive abilities).

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### Compliance with ethical standards

**Conflict of interest** JK has received consultancy or lecture fees from Zambon, UCB, Sanofi, Bial, Teva, Lundbeck, and research grants from CIBERNED, Instituto de Salud Carlos III, Fundació La Marató de TV3, Abbvie and Zambon. SMH declares no conflict of interest.

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