Chapter 8

# Cognitive Impairment in Parkinson's Disease: Historical Review, Past, and Present

Ivan Galtier, Antonieta Nieto and Jose Barroso

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/62888

**Abstract**

Parkinson's disease (PD) is a neurodegenerative disorder of unknown etiology, not only characterized by motor signs but also by non-motor symptoms, including neuropsychiatric and cognitive dysfunction. The results obtained in the last decades show that the cognitive changes in PD are heterogeneous; impairment in different cognitive domains such as attention, executive, language, memory, and visuospatial functions can be present even in the early stages of the disease. Mild cognitive impairment is frequent in non-demented PD patients and is considered as a risk factor for the development of dementia. As a response to the heterogeneity of cognitive impairment associated with PD, the Movement Disorders Society has recently developed formal diagnostic criteria for mild cognitive impairment and dementia associated with PD. In the present chapter, the authors have conducted a revision of cognitive impairment in PD, describing the results obtained in numerous investigations, from the first studies in the1970s to the advances of the last few years.

**Keywords:** Parkinson's disease, review, mild cognitive impairment, dementia, predictors variables

## 1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder of unknown etiology, characterized by tremor, rigidity, bradykinesia, and impairment of balance that are usually of an asymmetric course. The neuropathology of PD affects several structures that are implicated in movement control. The main neuropathologic feature of PD is the loss of dopaminergic neurons in the substantia nigra pars compacta, leading to a dysfunction of the frontostriatal system.

Ever since James Parkinson published his best known medical study, entitled "an essay on the shaking palsy" in 1817, this pathology has awakened scientific interest. Initially, most research effort focused on the understanding of motor symptoms and the search for effective treatment options. Levodopa, a precursor of dopamine, was discovered in the 1960s, and years later would be used as an effective treatment for the motor symptoms of PD. Coinciding with this historic landmark, a significant increase in interest in the non-motor symptoms associated with PD began to be observed, with special attention being paid to the cognitive symptoms, because of their impact on the quality of life of patients.

This chapter focuses on cognitive impairment in PD, from the first studies that paid attention to cognitive deficits to the present day concept of dementia associated to PD (PDD). There is a description of the neuropsychological profile classically associated with PD, going into the concept of mild cognitive impairment in PD (PD-MCI) in greater depth, which has given rise to numerous investigations in recent years. There is also a summary of the most relevant clinical and demographic variables associated with cognitive impairment in PD.

## 2. Cognitive impairment in PD: a historical review

### 2.1. First studies

PD is a neurodegenerative disorder described for the first time in 1817 by James Parkinson [1]. In the monographic entitled "an essay on the shaking palsy," the author described the clinical characteristics of a limited series of PD patients (Paralysis agitans). He defined the pathology as *"Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace"* and affirmed that *"the senses and intellects being uninjured"*. However, subsequent studies showed that the last statement is not correct.

Charcot [2], is among the first authors to describe changes in mental functioning in PD. The author stated that in PD patients *"…the mind becomes clouded and the memory is lost"*. However, it was not until the 1960s and 1970s, coinciding with the first levodopa treatments, that scientific interest of the cognitive disorders associated with this pathology increased significantly. Over the following years, and even during 1980s, investigations were carried out without excessive control over the clinical variables (cause of Parkinsonism, stage of disease, duration of illness, etc.). An example is the study of Reitan and Boll [3]. These authors selected a group of 25 PD patients and twenty five controls matched on sex, age, and education, which were evaluated with a battery of psychological tests. The results showed that PD patients suffered deterioration in general cognition, memory, problem-solving, abstract reasoning, and organizing abilities. This was a pioneer study in the use of a wide assessment of cognitive functions. However, information about the clinical features of the patients was not provided (disease stage, duration, motor symptoms, etc.).

The study of cognitive deficits associated with PD and other neurological diseases characterized by basal ganglia pathology, such as Huntington's disease and progressive supranuclear palsy, gave rise to the concept of subcortical dementia, as opposed to predominantly cortical

http://dx.doi.org/10.5772/62888

dementia characteristic of Alzheimer's disease [4, 5]. In this period, the concept of subcortical dementia is frequently associated in the literature with descriptions of cognitive impairment in PD. However, different authors consider that this label is often inaccurate and misleading because its application is not always suitable when referring to the cognitive impairment in PD; patients with PD may have cognitive deficits, without significantly affecting their daily lives [6, 7].

The discussions generated by the association between PD and the concept of subcortical dementia led to the development of numerous investigations with an increase in the interest in the control of clinical variables (disease stage, duration, motor symptoms, depression, etc.) and with more exhaustive neuropsychological evaluations [8–11]. The investigation conducted by Lees and Smith [12] is among the first studies to consider these characteristics. The authors conducted a careful sample selection according to the different variables related to the disease; they selected a sample of PD patients, in early-mid-stage of the disease (Hoehn and Yahr stage I–II), under 65 years of old, without depression and without antiparkinsonian drugs. The instruments administered included measures of general intelligence, executive functions, and memory. The PD patients only showed deficits in executive functions. Various investigations, such as the study of Lees and Smith [12], were performed in the 1980s and 1990s, and they led to the establishment of the neuropsychological profile classically associated with PD.

### 2.2. Neuropsychological profile of PD

Cognitive deficits in PD have traditionally been seen as an executive dysfunction secondary to frontostriatal system impairment. In this schema, this executive dysfunction is responsible for other cognitive disturbances that can appear in this pathology. However, the recently obtained results, in the last few decades, show that the cognitive changes in PD are more heterogeneous than initially thought. PD patients can have deficits in multiple cognitive domains including the executive functions but also in processing speed, attention, visuospatial functions, memory, and language. As will be seen below, the heterogeneity of cognitive impairment associated with PD cannot be explained exclusively as a consequence of dysexecutive syndrome.

PD is associated with cognitive slowing (bradyphrenia). Numerous studies have used reaction time tasks to evaluate processing speed and found that PD patients have deficits in simple and choice reaction time tests [13–18]. However, other investigations show that PD patients only present an altered execution in the choice reaction time task [19, 20]. The results of a meta-analysis conducted by Gauntlett-Gilbert and Brown [21] showed that patients exhibit an altered performance in simple and choice reaction time tasks, but the magnitude of the deficits was associated with the test complexity. This result has been explained in terms of a limitation of resources in tasks with more cognitive demands. Processing speed was also measured by Symbol Digit test and similar instruments; PD patients showed an altered execution with this type of test [22].

As regards attention and working memory, PD patients tend to perform normally in verbal tasks, such as digit span [22, 23], while their execution in visuospatial tasks is altered (visual

span) [23, 24]. Siegert et al. [25] conducted a meta-analysis including 56 studies. They differentiated the working memory tests according to the stimuli characteristic (verbal, visual) and difficulty level (direct, inverse). The results showed that PD patients performed poorly in all the working memory tasks. However, in the verbal tests, the difficulty was more significant in the more complex tasks (inverse), while patients showed significant difference in simple and complex tasks in visual tests. Other authors studied working memory based on the n-back paradigm and found that patients had deficits, compared to controls, unrelated to the level of demand or the nature of the stimuli [26].

Visuospatial functions tend to be altered in PD, even in the early stage of the disease. Different authors reported an altered performance in judgment of line orientation [23, 27], facial recognition test [28, 29], and visuospatial reasoning such as Raven's test [8, 10]. Block design [27–30] and the copy of Rey Complex figure test [27, 29] were other instruments in which PD patients showed poor execution. It should be noted that the motor component involving this type of tasks was not controlled in most of these investigations.

Executive functions include a complex set of processes that has been defined as wide and diverse. Lezak [31] define the executive functions as those skills to respond adaptively to novel situations: "*The executive functions can be conceptualized as having four components: (1) volition; (2) planning; (3) purposive action; and (4) effective performance. Each involves a distinctive set of activity-related behaviors. All are necessary for appropriate, socially responsible, and effectively self-serving adult conduct*" *(page 650)*.

The Wisconsin Cart Shorting Test (WCST) is one of the most widely used instruments for the assessment of executive functions; it measures the ability to form abstract concepts, develop strategies and use feedback to maintain or change the mental set on the objective. Numerous authors found that PD patients show an altered performance in this test, including less categories and a greater number of errors (e.g., see [32, 33]). Verbal fluency (VF) tests were also used to evaluate executive functions, as they are considered measures of cognitive flexibility and search strategy. Henry and Crawford [34] propose that phonetic fluency has more validity and specificity as a frontal impairment measure, compared with the WCST. The results obtained in PD with measures of VF are highly heterogeneous, both with phonetic and semantic fluency tests; different studies found an altered execution in PD patients [35–37], whereas other authors do not report the same results [38–40]. Henry and Crawford [41] studied the VF in PD by a meta-analysis that included 68 investigations and a total of 4644 participants. They found that PD is associated with a deficit in VF, with a greater involvement of semantic fluency in comparison with the phonetic fluency test. The difficulties are greater when versions of these tasks in which alternate consigns are used. According to the authors, the performance in VF in PD patients is not exclusively attributable to a deficit of executive functions (according to scores on the WCST); the relationship between the deficit of denomination task and VF performance suggests that PD is associated with a deficit in the recovery of information from semantic memory. Furthermore, the action fluency test has been considered an alternative VF measure of executive functions, since verb generation is strongly associated with the prefrontal cortex. PD patients show a poor performance with this task compared to controls [42].

http://dx.doi.org/10.5772/62888

Other instruments used to evaluate the executive functions in PD are the Trail Making Test (part B) and the Stroop test. As for the Trail Making Test, PD patients often have an altered performance [13, 19, 27]. However, with respect to the Stroop test, the results are heterogeneous: some authors report an altered performance in PD patients [15, 37, 43], whereas other research studies do not describe the same results [20, 22].

Regarding memory deficits in PD, classical descriptions consider that the alterations are confined to new information acquisition and spontaneous retrieval; the patients would show a normal performance in cued recall and recognition tasks. However, the results obtained in different investigations confirm that the affectation of memory functions in PD is more complex. PD patients often show an altered performance in different memory tests (Verbal Paired Associates, Logical Memory) [6, 44, 45], with a normal execution in recognition [44]. However, patients can perform poorly, compared to controls, even in recognition memory tasks [6]. Using tasks that allowed a more precise examination of different memory components (e.g., the Auditory Verbal Learning Test and the California Verbal Learning Test), some authors reported deficits in learning and spontaneous recall, without alteration in recognition [27, 37, 46]. However, this impairment pattern was not confirmed by other authors who found alterations in cued recall and recognition [47–50]. Whittington et al. [51] conducted a meta-analysis and concluded that PD patients have recognition deficits. Therefore, alteration of the verbal memory in PD is not exclusively limited to a deficit of information retrieval.

In regard to visual memory, there are fewer studies than those which are focused on verbal memory. The results obtained are diverse, probably as a consequence of the wide range of instruments used (Visual Retention Test, Visual Paired Associates, Face Memory Test, Complex Figure Test, etc.) [27, 45, 46, 52]. Visuospatial learning has been evaluated by Pillon et al. [53, 54] who found that PD patients present an altered execution. This result was confirmed in a more recent research study [23].

The first research studies into language functions in PD considered that the linguistic deficits observed in patients were a consequence of motor symptoms. Speech disorders were associated to alterations of phonation, facial musculature, reflections, articulation, and prosody [55–57]. However, in addition to the deficits described above, other alterations related to language production and comprehension are common in PD patients. The results of different studies show alterations in speech related to a lower proportion of sentences which are grammatically less complex [58–60]. On the other hand, the results obtained with the Boston naming test are not conclusive: some authors show an altered execution [8, 61], whereas other studies do not observe the same results [6, 44, 62]. Other investigations have been focused on the differentiation between the naming of actions and objects, based on the association of action generation with the frontal cortex. PD patients showed an altered performance in both naming tasks (naming and action), but the execution in the action naming was poorer than the naming of objects [63–65].

As for language comprehension in PD, it is worth mentioning the research line developed by the Grossman group. They reported the following results in a series of publications: patients had a normal performance in simple sentences and a deficient execution in complex sentences, with greater difficulty in those with subordinate clauses; patients show more difficulty

when analyzing sentences with subordinate clauses, when the semantic information does not allow their understanding; patients make more mistakes in tasks requiring the matching of a sentence with a picture and patients show deficits when identifying phonetic errors in grammatical morphemes, such as pronouns. Taking all the results together, the authors concluded that PD patients show deficit in language comprehension, related to the limitation of cognitive resources including, attention, cognitive slowing and working memory [66–70]. However, other results do not confirm the conclusions of Grossman [66]. Skeel et al. [62] showed that the alterations of comprehension can be present even in simple sentences and that this deficit was not associated with the status of working memory. Other authors have recently described similar results to Skeel et al. [62]; Galtier et al. [47] reported deficits in language comprehension that cannot be exclusively explained by a limitation of cognitive resources.

In summary, the results obtained in a large number of research studies over the last 40 years confirm that the cognitive deficits associated with PD are heterogeneous, including alterations in different cognitive domains such as attention, memory, executive functions, language, and visuospatial functioning. In addition, these data also confirm that the cognitive alterations in PD patients cannot be exclusively reduced to an executive dysfunction, as has traditionally been thought.

## 3. Mild cognitive impairment in PD

### 3.1. Concept of PD-MCI

Reisberg et al. [71] published the Global Deterioration Scale (GDS) in 1982 describing seven stages from normal to severe dementia associated with Alzheimer's disease. The GDS differentiates between stage 2 in which persons complain of memory deficits (without objective evidence in clinical interview, in employment or social situations) and stage 3 which was initially termed "mild cognitive decline". Clinical deficits appear in stage 3 although the objective evidence of memory deficit is only obtained by means of an intensive interview conducted by a clinician. In addition, decreased performance becomes manifest in demanding employment and social situations. Stage 3 is different to a GDS 4 stage which is considered as the earliest stage of dementia. Deficits are manifest in many areas in stage 4 and patients can no longer perform complex tasks accurately and efficiently. A cross-sectional study in 1988 used the terminology "mild cognitive impairment" (MCI) for the first time to refer the GDS stage 3 [72]. The results showed that MCI patients performed poorly in different cognitive measures, compared to GDS stage 2 subjects group (subjective deficits only). In addition, the group with mild dementia (GDS stage 4) performed significantly more poorly than the MCI group in the Mini-Mental State Examination and other cognitive measurements.

The concept of MCI was developed and popularized years later by Petersen et al. [73] who proposed the following diagnostic criteria: (1) memory complaint, preferably corroborated by an informant; (2) objective memory impairment; (3) normal general cognitive function; (4) intact activities of daily living; (5) not demented. The International Working group on Mild

http://dx.doi.org/10.5772/62888

Cognitive Impairment statement in 2004 recommended the criteria which are currently accepted [74] (**Table 1**).

| **Inclusion criteria** |
|---|
| • Not normal, not demented [does not meet criteria (DSM IV, ICD 10) for a dementia syndrome] |
| • Cognitive decline: |
| -Self and/or informant report and impairment on objective cognitive tasks |
| *And/or* |
| -Evidence of decline over time on objective cognitive tasks |
| • Preserved basic activities of daily living and minimal impairment in complex instrumental functions |

Adapted with permission from Winblad et al. [74]. © 2004 Blackwell Publishing Ltd.

**Table 1.** General criteria for MCI.

The construct of MCI in PD (PD-MCI) is a more recent concept, as a result of the gradual increase of interest in non-motor symptoms, the heterogeneity of cognitive deficits, and their impact on the quality of life of PD patients. The investigation of Janvin et al. [75] was the first study that focused on PD-MCI; it included 76 PD patients who were evaluated with a limited selection of neuropsychological tests (Benton Visual Retention Test, Judgment of Line Orientation test, Stroop Word Test). Forty-two patients had PD-MCI (55%), defined as scoring −2 standard deviations below the mean of the control group in at least one of the tests. In the PD-MCI group, 57% of the patients had an altered performance in one neuropsychological test, 33% in two tests while the remaining 10% had an altered execution in all the three tests.

In a recent review conducted by Litvan et al. [76], the authors reported that between 18.9% and 38.2% of PD patients met MCI criteria. However, the study of Janvin et al. [75], described above, and other investigations have reported results with higher percentages (51–55%) [77, 78]. These discrepancies can be explained by differences in the PD-MCI diagnostic criteria, number of cognitive domains explored or selection and number of neuropsychological tests used. Several studies used a less restrictive level (−1 standard deviation) to determine cognitive impairment, while other authors opted for a −1.5 standard deviation or −2 standard deviation cut-off. For example, Foltynie et al. [79] evaluated a group of 159 PD patients with different cognitive tests, including a pattern recognition memory, spatial recognition memory and the Tower of London task from the CANTAB battery. The results showed that 36% of PD patients were considered cognitively impaired, defined as scoring ≥1 standard deviation below the normative mean of at least one of the tests. Janvin et al. [80] conducted a study of cognitive function in a sample of 145 PD patients. Subjects with Mini-Mental State Examination score <25 were considered demented and excluded. Of the total sample, 72 PD patients without dementia were studied and compared to 38 normal controls. Of the nondemented PD patients, 52.8% were diagnosed with MCI, defined as impaired performance [−1.5 standard

deviation or more below the mean of the control group) in one, two, or all three of the given neuropsychological tests (Benton Visual Retention Test, Judgment of Line Orientation test, Stroop Word Test). In the study of Muslimovic et al. [81], the authors opted for a −2 standard deviation cut-off. They assessed a sample of 115 nondemented newly diagnosed PD patients with neuropsychological tests which examined the following six cognitive domains: psychomotor speed, attention, language, memory, executive functions, and visuospatial. Cognitive dysfunction was considered to be present whether performance in three or more neuropsychological tests was impaired. The results showed that 27 PD patients (23.5%) had cognitive dysfunction.

As one can see, there has been no consensus on the number of tests that need to be considered as altered to establish a diagnosis of MCI; alteration in one or more tests was taken as a criterion for the diagnosis of MCI [80], while other authors consider that impairment should be present in at least three tests (either within a single cognitive domain or across different cognitive domains) [81]. Moreover, most of the studies used brief batteries or a set of neuropsychological tests that do not allow the evaluation of all cognitive domains with a sufficient level of accuracy. Some authors described cognitive impairment as defined by poor performance in a selection of tests from the CANTAB battery (pattern recognition memory, spatial recognition memory and the Tower of London task) [82]. Other research only evaluated four cognitive domains, including memory, executive, attention, and visuospatial. Only one test was used for the case of memory and attention. Moreover, visuospatial function was examined by one item of the Montreal Cognitive Assessment test, which is a screening instrument [83]. Muslimovic et al. [81] selected a wide range of neuropsychological tests to examine cognitive functions in the following six domains: psychomotor speed, attention, language, memory, executive functions, and visuospatial/constructive skills. However, not all the domains were studied in the same degree of detail; although the memory and executive domains were investigated in depth by up to six tests, only the Boston Naming Test was used for the language examination.

### 3.2. Diagnostic criteria for PD-MCI

As a response to the heterogeneity mentioned above, the Movement Disorder Society (MDS) commissioned a task force to develop formal diagnostic criteria for PD-MCI which were published in 2012 [84]. The criteria proposed by the MDS are intended to overcome most of the previously described limitations. The MDS task force proposes a uniform method to characterize and diagnose PD-MCI, providing a framework to advance the understanding of this pathology. The proposal of the task force sets out new objectives for the following years (**Table 2**).

**I. Inclusion criteria**

- Diagnosis of Parkinson's disease as based on the UK PD Brain Bank Criteria [124]
- Gradual decline, in the context of established PD, in cognitive ability reported by either the patient or informant, or observed by the clinician

http://dx.doi.org/10.5772/62888

- Cognitive deficits 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

**II. Exclusion criteria**

- Diagnosis of PD dementia based on MDS Task Force proposed criteria [123]
- 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

Adapted with permission from Litvan et al. [84]. © 2012 Movement Disorder Society.

**Table 2.** MDS Criteria for the Diagnosis of PD-MCI.

The MDS criteria included a two-level operational schema that differs in the comprehensiveness of the neuropsychological testing. Level 1 criteria provide less diagnostic certainty than level 2: (A) Impairment on a scale of global cognitive abilities or impairment on a limited battery of neuropsychological tests. When a limited battery of tests is performed, impairment must be present in at least two tests for a diagnosis of PD-MCI (level 1); (B) Comprehensive neuropsychological testing that includes two tests in each of the five cognitive domains (attention and working memory, executive, language, memory, and visuospatial). Impairment should be present in at least two tests, either within a single cognitive domain or across different cognitive domains (level 2). In addition, impairment in neuropsychological tests may be demonstrated by performance approximately 1–2 standard deviations below age, education, gender, and culturally appropriate norms; or a significant decline demonstrated in serial cognitive testing; or a significant decline from estimated premorbid levels.

As proposed by the MDS task force, classification of PD-MCI subtypes is important for research purposes and for exploring whether impairments in different cognitive domains have a different neurobiological substrate and course. Comprehensive neuropsychological testing is required (level 2) for the PD-MCI sub-types classification. The use of two tests in each cognitive domain for the level 2 category examines all cognitive domains equally, can increase sensitivity and allow full subtyping of PD-MCI. The presence of two altered tests within a single cognitive domain, with the other domains unimpaired, represents a single domain subtype. Whether at least one test in two or more cognitive domains is impaired, then PD-MCI should be subtyped as multiple domain. The proposed MDS criteria recommend not using amnestic or nonamnestic terminology. Instead, specification of the affected domains is preferable so that potential differences among subtypes may be better analyzed in futures studies.

Up to now, only a few studies have provided data with the MDS PD-MCI criteria. Broeders et al. [85] examined a group of 123 newly diagnosed PD patients and found that PD-MCI was present in 35% of cases, when level 2 was applied (comprehensive assessment). In a more recent investigation, Stefanova et al. [86], applying level 2 of the MDS criteria, examined 111 early

PD patients and 105 healthy matched control subjects; PD-MCI was present in 24% of the patients. The differences in percentages compared to the study of Broeders et al. [85] can be explained by the clinical characteristics of PD patients; Stefanova et al. [86] included patients in stage 1 (Hoehn and Yahr] while the patient sample of the Broeders et al. [85] study were in stages 1 and 2. Pedersen et al. [87] examined a sample of 182 PD patients (Hoehn and Yahr stage 1–2), applying level 1 (brief assessment) of the MDS criteria and found that 20.3% of patients met MCI criteria. Other authors evaluated patients who had a mean PD duration of 5.2 and 14.1 years and found that PD-MCI was present in 33–42.6% of the patients respectively, when level 2 was used [88, 89]. Recently, Galtier et al. [90] showed that 60.5% of the patients were diagnosed with PD-MCI according to level 2 MDS criteria. The percentage of PD-MCI in this study was slightly higher than that obtained in previous studies. These differences could be explained by the tests used to assess the linguistic domain. The authors included an assessment of language comprehension, unlike the methodology used in previous investigations. Most of the studies that applied the MDS task force criteria used −1.5 SD cut-off [85, 87, 89, 90]. Goldman et al. [91], using a cut-off of 2 SD below norms, reported that 61.8% of patients (mean PD duration of 9.3 years) were classified as PD-MCI with level 2 of the MDS criteria. The subtype categorization showed the high predominance of the multiple-domain PD-MCI with percentages of between 84 and 96% [90, 92, 93].

## 4. Relationship between cognitive impairment in PD and clinical variables

There are many research studies which have studied the relationship between cognitive impairment and potential predictor variables. Cognitive performance has been related to the neurological impairment, duration of illness, age at onset of PD, depressive symptoms and educational level, among others. As we shall see, the results are diverse which could once again be interpreted as a reflection of the heterogeneity of cognitive impairment in PD.

Regarding neurological impairment, different investigations have opted for correlation analysis and found that the degree of neurological impairment was associated with poor performance in visuospatial functions [28, 94], processing speed [95], working memory [24], procedural learning [37] and executive functions [96, 97]. However, other authors have not confirmed these results finding no relationship between the neurological impairment and different cognitive functions, such as processing speed [98], visuospatial functions [99], or procedural learning [100, 101]. Neither has an association with declarative memory [53, 100, 102] or linguistic functions (comprehension sentences, verbs generation) [67, 103–105] been found.

Other investigations compared PD patients with different levels of neurological impairment according to the Hoehn and Yahr scale. Although these studies are less frequent, patients with mid-late PD (according to Hoehn and Yahr stage) often present more affectation in different cognitive domains. The investigation conducted by Huber et al. [8] was one of the first studies

http://dx.doi.org/10.5772/62888

that examined cognitive performance by comparing patients with different stages of PD. Moderate-to-late stage patients performed poorly in visuospatial functions, memory, executive functions, and naming. The results of Huber et al. [8] are clear evidence that the deterioration in the PD is not homogeneous, but that it is linked to the severity of the disease. Other authors also found differences in cognitive functions related to neurological impairment. For example, late disease stage patients showed poor performance in immediate memory (verbal and visual) [106], and executive functions (alternating series) [20].

Quite a few investigations pay attention to the relationship between illness duration and cognitive impairment. Research studies using correlation analysis showed that disease duration was not associated to processing speed [95, 98], working memory [10, 102], procedural learning [37], visuospatial functions [107], executive functions [10, 96], or sentence comprehension [67, 108, 109]. The results are more heterogeneous for other cognitive functions such as memory; some authors showed that disease duration was related to poor performance in diverse memory tests [10], while others did not find similar results [53, 110].

Other authors have demonstrated that cognitive dysfunction occurs even at the time of PD diagnosis. Foltynie et al. [79] showed that 36% of newly diagnosed PD patients had signs of cognitive impairment based on their performance in a pattern recognition memory task and in the Tower of London task. Similarly, Muslimovic et al. [81] examined a sample of newly diagnosed PD patients and found poor performance in different cognitive tasks; the differences when compared to normative data could mainly be explained by measures of immediate memory and executive function.

The age at onset of the disease has been associated with an increased risk of cognitive impairment, in other words the older the age at onset, the greater risk of cognitive decline, as measured with the Mini-Mental State Examination [111]. The study of relationship between age at onset of the disease and different cognitive functions revealed that the older the patient was at onset, the more likely the patient was to perform poorly in declarative memory (verbal and visual), executive, visuospatial and language functions (naming) [10, 15, 112, 113].

Depression is among the most common neuropsychiatric disturbances in PD. Different studies have concluded that between 36 and 60% of patients show depressive symptoms [114–116]. Numerous investigations have focused on the association between cognitive impairment and depression in PD. Depression has been associated with poor performance in global cognition, as measured by instruments such as the Mini-Mental State Examination or the Dementia Rating Scale [116–118]. Some authors who have studied the relationship between depressive symptoms and specific cognitive functions showed that depression was related to poor performance in different measures of executive functions [11] and in the comprehension of complex sentences [62]. However, other authors did not find any connection between depression and different cognitive functions, including processing speed [95], visuospatial functions [99], declarative memory [48], procedural learning [101], or sentence comprehension [67].

Certain authors have compared PD patients with and without depression by means of a comprehensive neuropsychological assessment. The results showed that patients with

depressive symptoms presented an altered performance in declarative memory and semantic fluency, without showing differences in verbal span, phonetic fluency, concept formation, or naming. However, when both groups of patients (with and without depression) were equated according to the Dementia Rating Scale no differences were found between the groups [119]. Ng et al. [120] recently looked into the influence of depression in cognitive functions using a longitudinal study. They examined eighty one PD patients who were classified into two groups; with and without depression, according to the score in the Geriatric Depression Scale (score ≥5 was required for depression diagnosis). The results showed that PD patients with depression had a slightly lower performance in global cognition, as measured by the Mini-Mental State Examination and the Montreal Cognitive Assessment test, although these differences did not reach statistical significance. On the other hand, no differences were found between patients with and without depression in a set of neuropsychological tests that included measures of attention, memory, executive, visuospatial, and language functions. An 18 month longitudinal study was conducted, and similar results to the baseline were found; both groups of patients did not differ in global cognition and cognitive measures. Therefore, although the depression in PD appears to have some effect on global cognition and some specific cognitive functions, the available results suggest that both depression and cognitive impairment evolve independently in this pathology.

As regards the study of clinical variables associated with PD-MCI, according to the new MDS task force criteria, the available data are still limited. The study of Pedersen et al. [87] found that patients with PD-MCI were older, had less education, longer disease duration and higher Hoehn and Yahr stage than patients without PD-MCI. Hobson and Meara [93] showed that PD-MCI was associated to increasing age and worsening motor function. Galtier et al. [90] reported that PD-MCI was associated with lower education and higher neurological impairment, as measured by the Hoehn and Yahr scale, although they did not find age of onset or duration to be important factors.

## 5. Dementia in PD

As we have seen in first section of the present chapter, the interest in dementia associated to PD patients dates back to the 1960s and over the last 30 years there have a large number of studies into the epidemiology of PDD. Aarsland et al. [121] conducted a review of 4336 patients in 27 studies and showed that the mean prevalence of PDD was 40%. The prevalence of dementia increased from 28% after 5 years of follow-up, to 48% at 15 years, and up to 83% after 20 years. Moreover, PDD has been associated with increased mortality; after 20 years of follow-up of newly diagnosed PD patients 100 of 136 (74%) have died [122].

The Movement Disorder Society (MDS) recruited a Task Force to define the clinical diagnostic criteria for PDD which were published in 2007 [123]. The defining feature of PDD is that dementia develops in the context of established PD. Hence, diagnosis of idiopathic PD (based on the UK PD Brain Bank Criteria) [124] before the development of dementia symptoms is the essential first step in the diagnosis. Diagnosis of dementia must be based on the

http://dx.doi.org/10.5772/62888

presence of deficits in at least two of the four core cognitive domains (attention, memory, executive, and visuospatial functions) as shown in clinical and cognitive examination, and be severe enough to affect normal functioning. Neuropsychiatric and behavioral symptoms are frequent, but are not invariable (**Table 3**). Clinical diagnostic criteria for probable and possible PDD are proposed by the MDS (**Table 4**).

---

**I. Core features**

**1.** Diagnosis of Parkinson's disease according to Queen Square Brain Bank criteria

**2.** A dementia syndrome with insidious onset and slow progression, developing within the context of established Parkinson's disease and diagnosed by history, clinical, and mental examination, defined as:

- Impairment in more than one cognitive domain
- Representing a decline from premorbid level
- Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms

**II. Associated clinical features**

**1.** Cognitive features:

- Attention: Impaired. Impairment in spontaneous and focused attention, poor performance in attentional tasks; performance may fluctuate during the day and from day to day
- Executive functions: Impaired. Impairment in tasks requiring initiation, planning, concept formation, rule finding, set shifting or set maintenance; impaired mental speed (bradyphrenia).
- Visuospatial functions: Impaired. Impairment in tasks requiring visual-spatial orientation, perception, or construction
- Memory: Impaired. Impairment in free recall of recent events or in tasks requiring learning new material, memory usually improves with cueing, recognition is usually better than free recall
- Language: Core functions largely preserved. Word finding difficulties and impaired comprehension of complex sentences may be present

**2.** Behavioral features:

- Apathy: decreased spontaneity; loss of motivation, interest, and effortful behavior
- Changes in personality and mood including depressive features and anxiety
- Hallucinations: mostly visual, usually complex, formed visions of people, animals or objects
- Delusions: usually paranoid, such as infidelity, or phantom boarder (unwelcome guests living in the home) delusions
- Excessive daytime sleepiness

**III. Features which do not exclude PD-D, but make the diagnosis uncertain**

- Co-existence of any other abnormality which may by itself cause cognitive impairment, but judged not to be the cause of dementia, e.g. presence of relevant vascular disease in imaging
- Time interval between the development of motor and cognitive symptoms not known

**IV. Features suggesting other conditions or diseases as cause of mental impairment, which, when present make it impossible to reliably diagnose PDD**

- The cognitive and behavioral symptoms appearing solely in the context of other conditions such as:

  Acute confusion due to

  **a.** Systemic diseases or abnormalities

  **b.** Drug intoxication

  Major Depression according to DSM IV

- Features compatible with "Probable Vascular dementia" criteria according to NINDS-AIREN

Adapted with permission from Emre et al. [123]. © 2007 Movement Disorder Society.

**Table 3.** Features of PDD.

**Probable PDD**

**1.** Core features: Both must be present

**2.** Associated clinical features:

- Typical profile of cognitive deficits including impairment in at least two of the four core cognitive domains (impaired attention which may fluctuate, impaired executive functions, impairment in visuo-spatial functions, and impaired free recall memory which usually improves with cueing)
- The presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports the diagnosis of Probable PDD, lack of behavioral symptoms, however, does not exclude the diagnosis

**3.** None of the group III features present

**4.** None of the group IV features present

**Possible PDD**

**1.** Core features: Both must be present

**2.** Associated clinical features:

- Atypical profile of cognitive impairment in one or more domains, such as prominent or receptive-type (fluent) aphasia, or pure storage-failure type amnesia (memory does not improve with cueing or in recognition tasks) with preserved attention
- Behavioral symptoms may or may not be present

OR

3. One or more of the group III features present

4. None of the group IV features present

Adapted with permission from Emre et al. [123]. © 2007 Movement Disorder Society.

**Table 4.** Criteria for the diagnosis of probable and possible PDD.

All epidemiological studies assessing the progression to dementia in PD have observed a high frequency of cognitive defects in patients without dementia; neuropsychological defects indicative of predominant posterior cortical dysfunction have been associated to dementia [125]. Along these lines, some investigations have examined whether cognitive performance in the first stages of the disease could predict the future development of dementia. The results obtained by different authors show that memory domain performance was a significant predictor to develop PDD [87, 90, 126, 127], although other cognitive domains such as attention [87], executive [128], visuospatial [82], and language [126] have also been identified as predictors of the development of dementia. Once again, these outcomes can be considered as evidence of the neuropathological heterogeneity associated with the evolution of PD. Over time, progression of cognitive impairment in PD is explained by the deterioration of the previously affected cognitive domains, but new symptoms and new cognitive defects seem to have a special impact on the conversion to PDD. In a longitudinal study, patients who developed PDD were characterized by the presence of defects in language functions; the comparison between patients with PDD, Alzheimer's disease, and dementia with Lewy bodies showed that the three groups had the same degree of difficulty in confrontation naming [129].

On the other hand, different clinical and demographic variables have been associated with the development of PDD and the most consistently reported are older age, lower education, greater severity of motor symptoms and REM sleep behavior disorder [126, 130–133]. Visual hallucinations have also been considered as a risk factor to develop dementia. In an 8-year prospective study, the presence of visual hallucinations at baseline proved a significant predictor of PDD [134]. A recent investigation with a sample of PD-MCI patients showed that 50% of patients with visual hallucinations developed PDD, in contrast to 25% of patients without hallucinations [135].

Recent studies have demonstrated that PD-MCI diagnosis is also associated with the development of dementia. The results described by different authors showed that patients who were diagnosed with PD-MCI have an increased risk of developing PDD in the years following diagnosis. In a 3 year longitudinal study with early PD patients, significantly more patients with PD-MCI than PD patients with normal cognition progressed to dementia; among patients with PD-MCI 27% developed PDD (annual progression rate of 9%), whereas only 0.7% of patients with normal cognition developed PDD [87]. Domellöf et al. [88] conducted a 5 year longitudinal study which included 115 PD patients with neuropsychological testing. Of the 115 patients, 31 (27%) developed PDD, which corresponds to an incidence rate of 62.6 per 1000 person-years. Forty-nine (42.6%) patients were classified as having MCI according to MDS

criteria, of which 25 (51%) developed PDD within 5 years, corresponding to an incidence rate of 142 per 1000 person-years. Similarly, Galtier et al. [90] showed that 42.3% of PD-MCI patients had dementia in a six to eight follow up study, whereas in the group of PD patients with normal cognition only 23.5% developed dementia during the follow up study. In addition, a 16 year longitudinal study showed that 91% of PD-MCI patients had progressed to PDD [93]. Santangelo et al. [136] examined 76 patients who underwent neuropsychological testing at baseline (Hoehn and Yahr stage 1–2), and at 2 and 4 years; 32.9% of PD patients had developed PD-MCI at baseline (level 2). No patient went from PD-MCI to dementia after 2 years, while 5.5% developed dementia after 4 years. The percentage of conversion to PDD is lower than that reported in previous studies. The authors considered that a possible explanation for this discrepancy might be found in the characteristics of our patients, who were relatively young and had mild disease severity compared to other studies stated above.

## 6. Conclusions

In summary, the study of cognitive functions in PD has awakened much scientific and research interest during the last 60 years. PD patients may even show cognitive deficits in the early stages of the pathology, as has been confirmed in studies with newly diagnosed patients. Cognitive impairment in PD is associated with alterations in different cognitive domains including deficits in attention, executive, memory, visuospatial and language functions. However, the heterogeneity in the manifestations and progression of these deficits is a characteristic of the pathology. In addition, different clinical and demographic variables have been linked to the evolution of cognitive impairment, with some of the most relevant being neurological impairment, disease duration, older age and educational level. Diagnostic criteria for PD-MCI and PDD have recently been developed and provide a uniform method to characterize the evolution of cognitive impairment in PD and advance the understanding of this pathology. The results demonstrate that PD-MCI is common in PD patients affecting around 25% in the first stages and increasing to over 50% according to the progression of the disease. Moreover, PD-MCI is considered a risk factor in the development of PDD, with a high conversion rate to dementia in the years following the PD-MCI diagnosis.

## Author details

Ivan Galtier*, Antonieta Nieto and Jose Barroso

*Address all correspondence to: igaltier@ull.edu.es

School of Psychology, University of La Laguna, Tenerife, Spain

http://dx.doi.org/10.5772/62888

## References

[1] Parkinson J. An Essay on the Shaking Palsy. London: Sherwood, Neely and Jones; 1817. 88 p.

[2] Charcot JM. [Lectures on the diseases of the nervous system]. 2° Edition. Paris: Delahaye et Lecrosnier; 1875.

[3] Reitan RM, Boll TJ. Intellectual and cognitive functions in Parkinson's disease. J Consult Clin Psychol. 1971;37(3):364–9.

[4] Cummings JL, Benson DF. Subcortical dementia. Review of an emerging concept. Arch Neurol. 1984;41(8):874–9.

[5] Huber SJ, Shuttleworth EC, Paulson GW. Dementia in Parkinson's disease. Arch Neurol. 1986;43(10):987–90.

[6] Levin BE, Llabre MM, Weiner WJ. Cognitive impairments associated with early Parkinson's disease. Neurology. 1989;39(4):557–61.

[7] Matthews CG, Haaland KY. The effect of symptom duration on cognitive and motor performance in parkinsonism. Neurology. 1979;29(7):951–6.

[8] Huber SJ, Freidenberg DL, Shuttleworth EC, Paulson GW, Christy JA. Neuropsychological impairments associated with severity of Parkinson's disease. J Neuropsychiatry Clin Neurosci. 1989;1(2):154–8.

[9] Pillon B, Dubois B, Lhermitte F, Agid Y. Heterogeneity of cognitive impairment in progressive supranuclear palsy, Parkinson's disease, and Alzheimer's disease. Neurology. 1986;36(9):1179–85.

[10] 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.

[11] Starkstein SE, Bolduc PL, Preziosi TJ, Robinson RG. Cognitive impairments in different stages of Parkinson's disease. J Neuropsychiatry Clin Neurosci. 1989;1(3):243–8.

[12] Lees AJ, Smith E. Cognitive deficits in the early stages of Parkinson's disease. Brain. 1983;106 (Pt 2):257–70.

[13] Akamatsu T, Fukuyama H, Kawamata T. The effects of visual, auditory, and mixed cues on choice reaction in Parkinson's disease. J Neurol Sci. 2008;269(1–2):118–25.

[14] Dubois B, Pillon B, Legault F, Agid Y, Lhermitte F. Slowing of cognitive processing in progressive supranuclear palsy. A comparison with Parkinson's disease. Arch Neurol. 1988;45(11):1194–9.

[15] Hietanen M, Teräväinen H. Cognitive performance in early Parkinson's disease. Acta Neurol Scand. 1986;73(2):151–9.

[16] Jahanshahi M, Brown RG, Marsden CD. Simple and choice reaction time and the use of advance information for motor preparation in Parkinson's disease. Brain. 1992;115 ( Pt 2:539–64.

[17] Jordan N, Sagar HJ, Cooper JA. Cognitive components of reaction time in Parkinson's disease. J Neurol Neurosurg Psychiatry. 1992;55(8):658–64.

[18] Kutukcu Y, Marks WJ, Goodin DS, Aminoff MJ. Simple and choice reaction time in Parkinson's disease. Brain Res. 1999 9;815(2):367–72.

[19] Camicioli RM, Wieler M, de Frias CM, Martin WRW. Early, untreated Parkinson's disease patients show reaction time variability. Neurosci Lett. 2008;441(1):77–80.

[20] de Frias CM, Dixon RA, Fisher N, Camicioli R. Intraindividual variability in neurocognitive speed: a comparison of Parkinson's disease and normal older adults. Neuropsychologia. 2007;45(11):2499–507.

[21] Gauntlett-Gilbert J, Brown VJ. Reaction time deficits and Parkinson's disease. Neurosci Biobehav Rev. 1998;22(6):865–81.

[22] Dujardin K, Denève C, Ronval M, Krystkowiak P, Humez C, Destée A, et al. Is the paced auditory serial addition test (PASAT) a valid means of assessing executive function in Parkinson's disease? Cortex. 2007;43(5):601–6.

[23] Galtier I, Nieto A, Barroso J, Lorenzo N. [Visuospatial learning impairment in Parkinson Disease]. Psicothema. 2009;21:21–6.

[24] Kemps E, Szmalec A, Vandierendonck A, Crevits L. Visuo-spatial processing in Parkinson's disease: evidence for diminished visuo-spatial sketch pad and central executive resources. Parkinsonism Relat Disord. 2005;11(3):181–6.

[25] Siegert RJ, Weatherall M, Taylor KD, Abernethy DA. A meta-analysis of performance on simple span and more complex working memory tasks in Parkinson's disease. Neuropsychology. 2008;22(4):450–61.

[26] Beato R, Levy R, Pillon B, Vidal C, du Montcel ST, Deweer B, et al. Working memory in Parkinson's disease patients: clinical features and response to levodopa. Arq Neuropsiquiatr. 2008;66(2A):147–51.

[27] Uc EY, Rizzo M, Anderson SW, Qian S, Rodnitzky RL, Dawson JD. Visual dysfunction in Parkinson disease without dementia. Neurology. 2005;65(12):1907–13.

[28] Bruna O, Roig C, Junqué C, Vendrell P. [Relationship between visuospatial impairment and oculomotor parameters in Parkinson's disease]. Psicothema. 2000;12:187–91.

[29] Sanchez Rodriguez JL. [Neuropsychological deficit in Parkinson's disease. Its relation with clinical variables]. Rev Neurol. 2002;35(4):310–7.

[30] Witt K, Nuhsman A, Deuschl G. Dissociation of habit-learning in Parkinson's and cerebellar disease. J Cogn Neurosci. 2002;14(3):493–9.

[31] Lezak MD. Neuropsychological Assessment. 3rd edition. New York: Oxford University Press; 1995.

[32] Liozidou A, Potagas C, Papageorgiou SG, Zalonis I. The role of working memory and information processing speed on Wisconsin card sorting test performance in Parkinson disease without dementia. J Geriatr Psychiatry Neurol. 2012;25(4):215–21.

[33] Paolo AM, Axelrod BN, Tröster AI, Blackwell KT, Koller WC. Utility of a Wisconsin card sorting test short form in persons with Alzheimer's and Parkinson's disease. J Clin Exp Neuropsychol. 1996;18(6):892–7.

[34] Henry JD, Crawford JR. A meta-analytic review of verbal fluency performance following focal cortical lesions. Neuropsychology. 2004;18(2):284–95.

[35] Bouquet CA, Bonnaud V, Gil R. Investigation of supervisory attentional system functions in patients with Parkinson's disease using the Hayling task. J Clin Exp Neuropsychol. 2003;25(6):751–60.

[36] Mimura M, Oeda R, Kawamura M. Impaired decision-making in Parkinson's disease. Parkinsonism Relat Disord. 2006;12(3):169–75.

[37] Muslimovic D, Post B, Speelman JD, Schmand B. Motor procedural learning in Parkinson's disease. Brain. 2007;130(Pt 11):2887–97.

[38] Brand M, Labudda K, Kalbe E, Hilker R, Emmans D, Fuchs G, et al. Decision-making impairments in patients with Parkinson's disease. Behav Neurol. 2004;15(3–4):77–85.

[39] Schneider JS. Behavioral persistence deficit in Parkinson's disease patients. Eur J Neurol. 2007;14(3):300–4.

[40] Troyer AK, Moscovitch M, Winocur G, Leach L, Freedman M. Clustering and switching on verbal fluency tests in Alzheimer's and Parkinson's disease. J Int Neuropsychol Soc. 1998;4(2):137–43.

[41] Henry JD, Crawford JR. Verbal fluency deficits in Parkinson's disease: a meta-analysis. J Int Neuropsychol Soc. 2004;10(4):608–22.

[42] Signorini M, Volpato C. Action fluency in Parkinson's disease: a follow-up study. Mov Disord. 2006;21(4):467–72.

[43] Hsieh Y-H, Chen K-J, Wang C-C, Lai C-L. Cognitive and motor components of response speed in the stroop test in Parkinson's disease patients. Kaohsiung J Med Sci. 2008;24(4): 197–203.

[44] el-Awar M, Becker JT, Hammond KM, Nebes RD, Boller F. Learning deficit in Parkinson's disease. Comparison with Alzheimer's disease and normal aging. Arch Neurol. 1987;44(2):180–4.

[45] Revonsuo A, Portin R, Koivikko L, Rinne JO, Rinne UK. Slowing of information processing in Parkinson's disease. Brain Cogn. 1993;21(1):87–110.

[46] Stefanova ED, Kostic VS, Ziropadja LJ, Ocic GG, Markovic M. Declarative memory in early Parkinson's disease: serial position learning effects. J Clin Exp Neuropsychol. 2001;23(5):581–91.

[47] Galtier I, Nieto A, Lorenzo JN, Barroso J. Cognitive impairment in Parkinson's disease: more than a frontostriatal dysfunction. Span J Psychol. 2014;17:1–8.

[48] Higginson CI, Wheelock VL, Carroll KE, Sigvardt KA. Recognition memory in Parkinson's disease with and without dementia: evidence inconsistent with the retrieval deficit hypothesis. J Clin Exp Neuropsychol. 2005;27(4):516–28.

[49] Kelly SW, Jahanshahi M, Dirnberger G. Learning of ambiguous versus hybrid sequences by patients with Parkinson's disease. Neuropsychologia. 2004;42(10):1350–7.

[50] Vingerhoets G, Vermeule E, Santens P. Impaired intentional content learning but spared incidental retention of contextual information in non-demented patients with Parkinson's disease. Neuropsychologia. 2005;43(5):675–81.

[51] Whittington CJ, Podd J, Kan MM. Recognition memory impairment in Parkinson's disease: power and meta-analyses. Neuropsychology. 2000;14(2):233–46.

[52] Uekermann J, Daum I, Peters S, Wiebel B, Przuntek H, Müller T. Depressed mood and executive dysfunction in early Parkinson's disease. Acta Neurol Scand. 2003;107(5): 341–8.

[53] Pillon B, Ertle S, Deweer B, Sarazin M, Agid Y, Dubois B. Memory for spatial location is affected in Parkinson's disease. Neuropsychologia. 1996;34(1):77–85.

[54] Pillon B, Deweer B, Vidailhet M, Bonnet AM, Hahn-Barma V, Dubois B. Is impaired memory for spatial location in Parkinson's disease domain specific or dependent on "strategic" processes? Neuropsychologia. 1998;36(1):1–9.

[55] Critchley EM. Speech disorders of Parkinsonism: a review. J Neurol Neurosurg Psychiatry. 1981;44(9):751–8.

[56] Ho AK, Iansek R, Bradshaw JL. The effect of a concurrent task on Parkinsonian speech. J Clin Exp Neuropsychol. 2002;24(1):36–47.

[57] Lloyd AJ. Comprehension of prosody in Parkinson's disease. Cortex. 1999;35(3):389–402.

[58] Cummings JL, Darkins A, Mendez M, Hill MA, Benson DF. Alzheimer's disease and Parkinson's disease: comparison of speech and language alterations. Neurology. 1988;38(5):680–4.

[59] Illes J, Metter EJ, Hanson WR, Iritani S. Language production in Parkinson's disease: acoustic and linguistic considerations. Brain Lang. 1988;33(1):146–60.

[60] Murray LL. Spoken language production in Huntington's and Parkinson's diseases. J Speech Lang Hear Res. 2000;43(6):1350–66.

[61] Goldman WP, Baty JD, Buckles VD, Sahrmann S, Morris JC. Cognitive and motor functioning in Parkinson disease: subjects with and without questionable dementia. Arch Neurol. 1998;55(5):674–80.

[62] Skeel RL, Crosson B, Nadeau SE, Algina J, Bauer RM, Fennell EB. Basal ganglia dysfunction, working memory, and sentence comprehension in patients with Parkinson's disease. Neuropsychologia. 2001;39(9):962–71.

[63] Bertella L, Albani G, Greco E, Priano L, Mauro A, Marchi S, et al. Noun verb dissociation in Parkinson's disease. Brain Cogn. 2002;48(2–3):277–80.

[64] Cotelli M, Borroni B, Manenti R, Zanetti M, Arévalo A, Cappa SF, et al. Action and object naming in Parkinson's disease without dementia. Eur J Neurol. 2007;14(6):632–7.

[65] Rodríguez-Ferreiro J, Menéndez M, Ribacoba R, Cuetos F. Action naming is impaired in Parkinson disease patients. Neuropsychologia. 2009;47(14):3271–4.

[66] Grossman M. Sentence processing in Parkinson's disease. Brain Cogn. 1999;40(2):387–413.

[67] Grossman M, Carvell S, Stern MB, Gollomp S, Hurtig HI. Sentence comprehension in Parkinson's disease: the role of attention and memory. Brain Lang. 1992;42(4):347–84.

[68] Grossman M, Kalmanson J, Bernhardt N, Morris J, Stern MB, Hurtig HI. Cognitive resource limitations during sentence comprehension in Parkinson's disease. Brain Lang. 2000;73(1):1–16.

[69] Grossman M, Zurif E, Lee C, Prather P, Kalmanson J, Stern MB, et al. Information processing speed and sentence comprehension in Parkinson's disease. Neuropsychology. 2002;16(2):174–81.

[70] Lee C, Grossman M, Morris J, Stern MB, Hurtig HI. Attentional resource and processing speed limitations during sentence processing in Parkinson's disease. Brain Lang. 2003;85(3):347–56.

[71] Reisberg B, Ferris SH, de Leon MJ, Crook T. The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry. 1982;139(9):1136–9.

[72] Reisberg B, Ferris SH, de Leon MJ, Franssen ESE, Kluger A, Mir P, et al. Stage-specific behavioral, cognitive, and in vivo changes in community residing subjects with age-associated memory impairment and primary degenerative dementia of the Alzheimer type. Drug Dev Res. 1988;15(2–3):101–14.

[73] Petersen RC, Stevens JC, Ganguli M, Tangalos EG, Cummings JL, DeKosky ST. Practice parameter: early detection of dementia: mild cognitive impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2001;56(9):1133–42.

[74] Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund L-O, et al. Mild cognitive impairment—beyond controversies, towards a consensus: report of the

International Working Group on Mild Cognitive Impairment. J Intern Med. 2004;256(3): 240–6.

[75] 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.

[76] 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.

[77] 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.

[78] Sollinger AB, Goldstein FC, Lah JJ, Levey AI, Factor S a. Mild cognitive impairment in Parkinson's disease: subtypes and motor characteristics. Parkinsonism Relat Disord. Elsevier Ltd; 2010;16(3):177–80.

[79] Foltynie T, Brayne CEG, Robbins TW, Barker R a. The cognitive ability of an incident cohort of Parkinson's patients in the UK. The CamPaIGN study. Brain. 2004;127(Pt 3): 550–60.

[80] Janvin CC, Larsen JP, Salmon DP, Galasko D, Hugdahl K, Aarsland D. Cognitive profiles of individual patients with Parkinson's disease and dementia: comparison with dementia with Lewy bodies and Alzheimer's disease. Mov Disord. 2006;21(3):337–42.

[81] Muslimovic D, Post B, Speelman JD, Schmand B. Cognitive profile of patients with newly diagnosed Parkinson disease. Neurology. 2005;65(8):1239–45.

[82] Williams-Gray CH, Foltynie T, Brayne CEG, Robbins TW, Barker R a. Evolution of cognitive dysfunction in an incident Parkinson's disease cohort. Brain. 2007;130(Pt 7): 1787–98.

[83] 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.

[84] Litvan I, Goldman JG, Tröster 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.

[85] Broeders M, de Bie RMA, Velseboer DC, Speelman JD, Muslimovic D, Schmand B. Evolution of mild cognitive impairment in Parkinson disease. Neurology. 2013;81(4): 346–52.

[86] Stefanova E, Žiropadja L, Stojković T, Stanković I, Tomić A, Ječmenica-Lukić M, et al. Mild Cognitive Impairment in Early Parkinson's Disease Using the Movement

Disorder Society Task Force Criteria: Cross-Sectional Study in Hoehn and Yahr Stage 1. Dement Geriatr Cogn Disord. 2015;40(3–4):199–209.

[87] Pedersen KF, Larsen JP, Tysnes O-B, Alves G. Prognosis of mild cognitive impairment in early parkinson disease: the Norwegian ParkWest Study. JAMA Neurol. 2013;70(5):580–6.

[88] Domellöf ME, Ekman U, Forsgren L, Elgh E. Cognitive function in the early phase of Parkinson's disease, a five-year follow-up. Acta Neurol Scand. 2015;132(2):79–88.

[89] Marras C, Armstrong MJ, Meaney C a., Fox S, Rothberg B, Reginold W, et al. Measuring mild cognitive impairment in patients with Parkinson's disease. Mov Disord. 2013;28(5):626–33.

[90] Galtier I, Nieto A, Lorenzo JN, Barroso J. Mild cognitive impairment in Parkinson's disease: diagnosis and progression to dementia. J Clin Exp Neuropsychol. 2016;38(1): 40–50.

[91] Goldman JG, Holden S, Bernard B, Ouyang B, Goetz CG, Stebbins GT. Defining optimal cutoff scores for cognitive impairment using movement disorder society task force criteria for mild cognitive impairment in Parkinson's disease. Mov Disord. 2013;28(14): 1972–9.

[92] Goldman JG, Holden S, Ouyang B, Bernard B, Goetz CG, Stebbins GT. Diagnosing PD-MCI by MDS Task Force criteria: how many and which neuropsychological tests? Mov Disord. 2015;30(3):402–6.

[93] Hobson P, Meara J. Mild cognitive impairment in Parkinson's disease and its progression onto dementia: a 16-year outcome evaluation of the Denbighshire cohort. Int J Geriatr Psychiatry. 2015;30(10):1048–55.

[94] Alegret M, Junqué C, Pueyo R, Valldeoriola F, Vendrell P, Tolosa E, et al. MRI atrophy parameters related to cognitive and motor impairment in Parkinson's disease. Neurol (Barcelona, Spain). 2001;16(2):63–9.

[95] Deroost N, Kerckhofs E, Coene M, Wijnants G, Soetens E. Learning sequence movements in a homogenous sample of patients with Parkinson's disease. Neuropsychologia. 2006;44(10):1653–62.

[96] Alevriadou A, Katsarou Z, Bostantjopoulou S, Kiosseoglou G, Mentenopoulos G. Wisconsin card sorting test variables in relation to motor symptoms in Parkinson's disease. Percept Mot Skills. 1999;89(3 Pt 1):824–30.

[97] Pereira JB, Junqué C, Martí MJ, Ramirez-Ruiz B, Bartrés-Faz D, Tolosa E. Structural brain correlates of verbal fluency in Parkinson's disease. Neuroreport. 2009;20(8):741–4.

[98] Morris RG, Downes JJ, Sahakian BJ, Evenden JL, Heald A, Robbins TW. Planning and spatial working memory in Parkinson's disease. J Neurol Neurosurg Psychiatry. 1988;51(6):757–66.

[99] Crucian GP, Barrett AM, Schwartz RL, Bowers D, Triggs WJ, Friedman W, et al. Cognitive and vestibulo-proprioceptive components of spatial ability in Parkinson's disease. Neuropsychologia. 2000;38(6):757–67.

[100] Vakil E, Herishanu-Naaman S. Declarative and procedural learning in Parkinson's disease patients having tremor or bradykinesia as the predominant symptom. Cortex. 1998;34(4):611–20.

[101] Sommer M, Grafman J, Clark K, Hallett M. Learning in Parkinson's disease: eyeblink conditioning, declarative learning, and procedural learning. J Neurol Neurosurg Psychiatry. 1999;67(1):27–34.

[102] Dalrymple-Alford JC, Kalders AS, Jones RD, Watson RW. A central executive deficit in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry. 1994;57(3):360–7.

[103] Colman KSF, Koerts J, van Beilen M, Leenders KL, Post WJ, Bastiaanse R. The impact of executive functions on verb production in patients with Parkinson's disease. Cortex. 2009;45(8):930–42.

[104] Crescentini C, Mondolo F, Biasutti E, Shallice T. Supervisory and routine processes in noun and verb generation in nondemented patients with Parkinson's disease. Neuropsychologia. 2008;46(2):434–47.

[105] Péran P, Rascol O, Démonet J-F, Celsis P, Nespoulous J-L, Dubois B, et al. Deficit of verb generation in nondemented patients with Parkinson's disease. Mov Disord. 2003;18(2):150–6.

[106] Whittington CJ, Podd J, Stewart-Williams S. Memory deficits in Parkinson's disease. J Clin Exp Neuropsychol. 2006;28(5):738–54.

[107] Girotti F, Soliveri P, Carella F, Geminiani G, Aiello G, Caraceni T. Role of motor performance in cognitive processes of Parkinsonian patients. Neurology. 1988;38(4): 537–40.

[108] Natsopoulos D, Grouios G, Bostantzopoulou S, Mentenopoulos G, Katsarou Z, Logothetis J. Algorithmic and heuristic strategies in comprehension of complement clauses by patients with Parkinson's disease. Neuropsychologia. 1993;31(9):951–64.

[109] Natsopoulos D, Katsarou Z, Alevriadou A, Grouios G, Bostantzopoulou S, Mentenopoulos G. Deductive and inductive reasoning in Parkinson's disease patients and normal controls: review and experimental evidence. Cortex. 1997;33(3):463–81.

[110] Flowers KA, Pearce I, Pearce JM. Recognition memory in Parkinson's disease. J Neurol Neurosurg Psychiatry. 1984;47(11):1174–81.

[111] Aarsland D, Andersen K, Larsen JP, Perry R, Wentzel-Larsen T, Lolk A, et al. The rate of cognitive decline in Parkinson disease. Arch Neurol. 2004;61(12):1906–11.

[112] Dubois B, Pillon B, Sternic N, Lhermitte F, Agid Y. Age-induced cognitive disturbances in Parkinson's disease. Neurology. 1990;40(1):38–41.

[113] Locascio JJ, Corkin S, Growdon JH. Relation between clinical characteristics of Parkinson's disease and cognitive decline. J Clin Exp Neuropsychol. 2003;25(1):94–109.

[114] Cummings JL. Depression and Parkinson's disease: a review. Am J Psychiatry. 1992;149(4):443–54.

[115] Shulman LM, Taback RL, Bean J, Weiner WJ. Comorbidity of the nonmotor symptoms of Parkinson's disease. Mov Disord. 2001;16(3):507–10.

[116] Rojo A, Aguilar M, Garolera MT, Cubo E, Navas I, Quintana S. Depression in Parkinson's disease: clinical correlates and outcome. Parkinsonism Relat Disord. 2003;10(1):23–8.

[117] Starkstein SE, Bolduc PL, Mayberg HS, Preziosi TJ, Robinson RG. Cognitive impairments and depression in Parkinson's disease: a follow up study. J Neurol Neurosurg Psychiatry. 1990;53(7):597–602.

[118] Cubo E, Bernard B, Leurgans S, Raman R. Cognitive and motor function in patients with Parkinson's disease with and without depression. Clin Neuropharmacol. 2000;23(6):331–4.

[119] Tröster AI, Stalp LD, Paolo AM, Fields JA, Koller WC. Neuropsychological impairment in Parkinson's disease with and without depression. Arch Neurol. 1995;52(12): 1164–9.

[120] Ng A, Chander RJ, Tan LCS, Kandiah N. Influence of depression in mild Parkinson's disease on longitudinal motor and cognitive function. Parkinsonism Relat Disord. 2015;21(9):1056–60.

[121] Aarsland D, Zaccai J, Brayne C. A systematic review of prevalence studies of dementia in Parkinson's disease. Mov Disord. 2005;20(10):1255–63.

[122] Hely MA, Reid WGJ, Adena MA, Halliday GM, Morris JGL. The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years. Mov Disord. 2008;23(6):837–44.

[123] 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 1837.

[124] Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry. 1992;55(3):181–4.

[125] 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.

[126] Hobson P, Meara J. Risk and incidence of dementia in a cohort of older subjects with Parkinson's disease in the United Kingdom. Mov Disord. 2004;19(9):1043–9.

[127] Levy G, Jacobs DM, Tang M-X, Côté LJ, Louis ED, Alfaro B, et al. Memory and executive function impairment predict dementia in Parkinson's disease. Mov Disord. 2002;17(6): 1221–6.

[128] Woods SP, Tröster AI. Prodromal frontal/executive dysfunction predicts incident dementia in Parkinson's disease. J Int Neuropsychol Soc. 2003;9(1):17–24.

[129] Noe E, Marder K, Bell KL, Jacobs DM, Manly JJ, Stern Y. Comparison of dementia with Lewy bodies to Alzheimer's disease and Parkinson's disease with dementia. Mov Disord. 2004;19(1):60–7.

[130] Gjerstad MD, Aarsland D, Larsen JP. Development of daytime somnolence over time in Parkinson's disease. Neurology. 2002;58(10):1544–6.

[131] Hughes TA, Ross HF, Musa S, Bhattacherjee S, Nathan RN, Mindham RH, et al. A 10-year study of the incidence of and factors predicting dementia in Parkinson's disease. Neurology. 2000;54(8):1596–602.

[132] Levy G, Schupf N, Tang M-X, Cote LJ, Louis ED, Mejia H, et al. Combined effect of age and severity on the risk of dementia in Parkinson's disease. Ann Neurol. 2002;51(6): 722–9.

[133] Mahieux F, Fénelon G, Flahault A, Manifacier MJ, Michelet D, Boller F. Neuropsychological prediction of dementia in Parkinson's disease. J Neurol Neurosurg Psychiatry. 1998;64(2):178–83.

[134] Aarsland D, Andersen K, Larsen JP, Lolk A, Kragh-Sørensen P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol. 2003;60(3):387–92.

[135] Gasca-Salas C, Clavero P, García-García D, Obeso JA, Rodríguez-Oroz MC. Significance of visual hallucinations and cerebral hypometabolism in the risk of dementia in Parkinson's disease patients with mild cognitive impairment. Hum Brain Mapp. 2016;37(3):968–77.

[136] Santangelo G, Vitale C, Picillo M, Moccia M, Cuoco S, Longo K, et al. Mild cognitive impairment in newly diagnosed Parkinson's disease: a longitudinal prospective study. Parkinsonism Relat Disord. 2015;21(10):1219–26.