Neuropsychological Features of Mild Cognitive Impairment in Parkinson's Disease: A Critical Review of the Literature

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Abstract: Motor features traditionally define Parkinson's disease (PD), but non-motor characteristics such as cognitive impairment and dementia have been gradually documented as a core part of PD. Mild cognitive impairment, as a pre-dementia phase of cognitive dysfunction, is recognised as common in non-demented PD patients. In any case, before Parkinson's Disease-Mild Cognitive Impairment (PD-MCI) diagnostic criteria proposed by the Movement Disorder Society (MDS) Task Force in 2012, there was no agreement in the scientific community about definition, clinical features and evolution of PD-MCI. It explains why epidemiological data reported by many studies provide contrasting results. Nevertheless, many investigations have pointed out that a large amount of PD patients without dementia present a specific neuropsychological impairment, mainly characterized by executive, visuospatial and memory deficits. This review focuses on mild cognitive impairment in PD (PD-MCI). To clarify the characterization of PD-MCI neuropsychological profile, a MEDLINE literature search was carried out. Data were extracted from studies published since 1980. The neurocognitive profile of PD patients was heterogeneous. Cognitive impairment was common in PD even at the time of diagnosis and before drug treatment and it was associated with functional impairment. Primary findings reported that single domain impairment with executive dysfunction was more common than multiple domain impairment, but, nowadays, those results are largely criticized. Moreover, visual-space abilities deteriorated very early during the pathology. Patients with posterior cortical deficits seemed to be associated with the development of Parkinson's Disease Dementia (PD-D), whereas patients with front striatal deficits were not, hence suggesting the presence of two distinct cognitive syndromes with different aetiologies and prognoses. However, several questions regarding PD-MCI criteria remain currently unanswered. More attention must be paid to the definition of best cut-off scores and to accurate, specific and sensitive tests for discriminating between patients with and without PD-MCI. Further investigations should define the exact prevalence of PD-MCI across different sites/cohort types, estimate PD-MCI subtypes prevalence and even link the clinical phenotype (akinetic-rigid vs tremor-dominant) to the different neuropsychological profiles. Furthermore, research needs to focus on detecting the neuropsychological predictors of PD-MCI conversion into PD-D. Poor efficacy of non-pharmacological intervention to delay the onset of PD-D in PD-MCI patients is also discussed.

Keywords: Parkinson's disease, mild cognitive impairment, diagnostic criteria, epidemiology, neuropsychology, assessment, non-pharmacological treatment.

INTRODUCTION

Historically, James Parkinson was the first to describe Parkinson's disease (PD) in 1817. According to the author [1] in PD "the senses and intellects being uninjured". At a later stage, Charcot [2], the researcher who renames the illness in honor of James Parkinson, asserts "the mind becomes clouded and the memory is lost". He was the first to recognize how PD subjects had not only motor, but a cognitive (at the time, labelled intellectual) involvement as well. In light of more recent evidence, it has become clearer that not only motor but also cognitive and affective deficits characterize PD. Successive studies focus on dementia risk factors individuation, in fact, PD patients with cognitive deficits have more probability to develop dementia when compared to control groups [3-5]. According to Aarsland [6] from the time of diagnosis, PD patients with cognitive impairment have double the risk to develop dementia than control groups. Furthermore, a part of the scientific literature revealed a predictive association between executive dysfunctions [7,8] verbal fluency [9], visual-spatial deficits [7,10] and the development of dementia in PD patients. Nowadays, Parkinson's Disease Dementia (PDD) is described by the Diagnostic and Statistical Manual of Mental Disorder V Edition as a condition in which evidence of significant decline from a previous level of performance is present, based on the concern of the individual or an informant and confirmed by standardized neuro-psychological testing. The cognitive deficit must interfere with independence in everyday activities and must occur in the setting of established PD [11]. From the Nineties the term "Mild Cognitive Impairment" (MCI) has become usual even in PD: researchers and clinicians used this nosographic entity borrowed from Petersen's theoretical model to describe the slight cognitive deficits also affecting PD subjects [7,8,12,13]. To identify the intermediate stage between minor cognitive changes in healthy ageing and dementia,

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E-ISSN: 2309-6128/14

several definitions have been suggested. Currently, the term "Mild Cognitive Impairment (MCI)" detects this transitional stage. The construct of MCI has evolved over the past decade since the MCI definition in 2004 [14]. According to Petersen [15] MCI refers to an inhomogeneous clinical syndrome with multiple etiologies, whereas the first definition of MCI Petersen [16] was openly focused on memory deficits, in order to individuate the prodromal signs of Alzheimer's disease (AD). Today, in addition to memory, MCI criteria include impairment in other cognitive domains. Such a diagnostic label is currently also used for PD patients to indicate a transitional period between normal cognitive functioning and the onset of Parkinson's disease dementia (PDD). Thus, the construct of MCI has increasingly become more relevant for the identification of early cognitive deficits to set up early therapeutic interventions both psychological and pharmacological.

MATERIALS AND METHODS

A systematic literature search (PubMed, Cochrane Library) on Mild Cognitive Impairment in Parkinson's disease was performed. The time limit used in the search was from 1980 to 2014 and keywords were "Parkinson's disease", "mild cognitive impairment", "epidemiology", "neuropsychological testing", "non-pharmacological treatment" and "cognitive rehabilitation". We found 452 references using the terms "Parkinson's disease", "mild cognitive impairment", 80 with "Parkinson's disease" and "mild cognitive impairment" and "epidemiology", 221 with "Parkinson's disease" and mild cognitive impairment and neuropsychological testing, 26 with "Parkinson's disease", "mild cognitive impairment", and "non pharmacological treatment". Only one interesting paper was found by using "Parkinson's disease" and "mild cognitive impairment" and "cognitive rehabilitation" in the Cochrane Reviews. Manuscripts were excluded if individuals other than ones with mild cognitive impairment had been recruited to be assessed, if they were case studies or referred to integrated treatments (pharmacological *plus* non-pharmacological). This screening has yielded 146 articles to be evaluated.

RESULTS

Epidemiology

To date, epidemiological data on cognitive impairment in PD are very few and contrasting, depending on the high heterogeneity of inclusion/exclusion criteria, evaluation procedures and clinical settings in which patients were enrolled. For these reason, the frequency of PD patients with cognitive impairment varies from 19% to 25% [17-20]. Starting from the new MCI criteria publication and diffusion in the scientific community [14], such label also becomes usual for non-demented PD patients, as well. However, a uniform and formal diagnosis for PD-MCI has been possible only starting from MDS criteria publications in 2012 [21]. Articles we presented precede this date. In the CamPaIGN study, [22] drawn for the new PD cases in the UK incidence's estimation, the 36% of PD subject newly diagnosed can also be classified as MCI. This percentage was lower in the Norwegian Park West Study, for which only 18.9% of patient presented MCI [6]. Conversely, one study recruiting subjects with a 4-year PD diagnosis, estimated a percentage of 55% of non-demented individuals presenting MCI in a cohort of 103 patients [12]. In summary, according to Dalrymple-Alford, 14 to 89 percent of PD subjects can be classified as MCI, depending on the methodology of research and populations being studied [17]. Epidemiological studies upon MCI subcategories in PD patients are very recent. According to the Park West Study's incident cohort, 67% of the individuals were categorised as non-amnestic single domain. Amnestic single domain reached 24.3% and multiple domain 10.8% [6]. Prevalence studies showed similar results. In 2007, Caviness reported that single domain is more common than multiple domains. In both groups, the most damaged domain was the executive one, followed by the amnesic one. In particular, the distribution was as follows: non-amnestic single domain > amnestic single domain = non-amnestic multiple domains > amnestic multiple domain [19]. According to the firsts studies of Litvan [23], epidemiological data globally demonstrated how single domain damage is more common than the multiple domain one; in the single domain, non-amnestic subtype is more common than the amnestic one.

Neuropsychological Profile of PD Subjects without Dementia

The following studies serve to update scientific literature about the neuropsychological profile of cognitive impairment no-dementia PD subjects. The terminology "PD-MCI" is not methodically presented in the studies, where often the terms "non-demented PD patients", "cognitive impairment no dementia" or "PD subjects with cognitive impairment" are utilised; conversely, "PD-MCI" becomes a term systematically used only since the recent diagnostic criteria publication [21]. All the studies presented below precede Litvan's criteria publication and formal PD-MCI

definition [21]. Studies whose aim was to systematically describe the neuropsychological impairment of non-demented subjects with Parkinson's disease can be found in scientific literature since the Eighties. Cognitive deficits occurring in PD are related to processing speed, visual-spatial skills, verbal fluency, memory and executive functions [12,24,25]. According to Caviness *et al.* [19], the investigation on cognitive functioning of PD patients should be limited to memory and executive functioning that are the most impaired subdomains. Furthermore, it has been assumed that the whole range of deficits observed in patients with PD might be explainable by a frontal hypothesis [26,27], that assumes a similar neuropsychological profile of PD patients and subjects with frontal syndromes. In recent years, attention towards executive deficits in non-demented patients with PD, has considerably increased [28-32]. Currently, executive functioning impairment is recognised to be the most precocious cognitive impairment occurring in PD [25]. Problems in cognitive flexibility, planning and working memory have been pointed out in many studies [33-36]. According to the updated literature, performance of non-demented subjects with Parkinson's disease results poor in cognitive tasks requiring the implementation of spontaneous strategies for information processing [36-39]. Difficulties in attention also appear to be very common [40]. For example, in backward digit-span tests, the performance is generally worse than in forward digit-span tests. This may be due to the different nature of the second type of tests, based uniquely on immediate recall processes [41]. Memory deficits observed in PD patients reflect recall deficit for recently acquired information. Difficulties in free recall as opposed to guided recall or to recognition tasks have been pointed out by one study [40]. Moreover, patients involved in guided recall tasks of verbal material get better performances if they are given a semantic cue [42]. Much evidence suggests how memory deficit may be mainly due to a primitive executive dysfunction. The recall deficit is also highlighted by the poor utilisation of semantic strategies during verbal fluency tasks [43,44]. Some researchers also reported deficits in encoding processes, [45,46]. Deficits in consolidation and intrusion errors, very common in subjects with Alzheimer's disease, become noticeable in patients with Parkinson's disease only with the development of dementia [47,48]. PD patients also show slowness in acquiring new information [49,50]. Working memory turns out to be one of the cognitive domains mostly affected in PD subjects [30,51-54]. While slave systems of working memory seem to be intact [55], the executive process operating on them would show a deficit [56]. Bradley *et al.* [52] found that patients with mild or moderate Parkinson's disease have deficits in visual-spatial working memory tests, but not in verbal working memory tests. This finding was confirmed by other investigations [31,55]. According to Le Bras [57], discrepancy may be explained by the different level of involvement in the spatial processing, a widely documented deficit of PD subjects [58]. The performance would result worse because of a primitive visual-spatial deficiency, and not because of a pure working memory deficit. PD patients test poorly in learning new motor, perceptual or cognitive tasks [59-61], while priming does not show any deficits. According to Ferraro [62] and Jackson [63], non-demented subjects with Parkinson's disease show worse performances than control subjects in cognitive tasks requiring procedural learning. In particular, given the nature of the task, this is probably due either to a deficit in learning the chronological order of the information or to a deficit in expressing such order. Smith [64] compared the results on Serial Reaction Time (SRT) and on an artificial grammar-learning test. The experimental hypothesis was based on the expectation that PD subjects would have a good performance only in learning the artificial grammar. In fact, the SRT is a test supposedly based on the functioning of cerebral regions such as the basal ganglia, an area damaged in PD and involved in motor sequences. Nevertheless, in both tests PD patients did not turn out to be significantly different from the control subjects, implying a re-check of SRT functioning. Moreover, several authors have pointed out the presence of dysfunctions in prospective memory in PD patients [65-71]. Katai *et al.* [72,73] noticed that deficit is essentially based on a dysfunction in event-based mechanism of prospective memory. The purely retrospective part (*what to recall*) seems to be preserved. According to Foster [70], in PD subjects prospective memory deficits are more noticeable when the recall cue is not crucial despite to the interfering activity at which the subject is exposed during the cognitive task. Such findings should suggest an executive discontrol in monitoring and attentional shifting. Non-demented patients with PD have better performance when they focus on the one to be recalled [74]. Raskin [75], by opposite, showed a worse performance of PD patients in time-based as opposed to event-based prospective memory tasks. The study also documented a relationship between the executive measures, such as inhibition, planning and strategic research abilities, and performances in time-based prospective memory tasks. With regard to the language domain, PD patients often suffer from hypophonia and

dysarthria. Aphasic and paraphasic problems are rarely present in PD contrary to Alzheimer's disease. PD patients may have deficits in comprehension and production of complex syntactical structures [76,77], while comprehension of texts seems to be globally preserved [78]. Moreover, a semantic fluency deficit for non-demented PD patients has been recently shown [79]. The analysis of the performance of tasks that focus on verbal fluency, where patients with Parkinson's disease show more deficits, turns out to be more complex. These results might be the consequence of a deficit in the use of verbal recall strategies such as clustering or switching [80], that specifically represent the ability to regroup words based on their sound or semantic category, and the ability to effectively switch between sounds or categories, respectively. In other words, poor performances on fluency tests may be not only based on a linguistic deficit. Finally, cognitive deficits in visual-perceptual tasks represent an early neuropsychological feature of PD patients [81]. Nevertheless, many authors take into consideration a set-shifting deficit in spatial memory, mainly caused by bradyphrenia, to explain these deficits [82,83]. However, PD patients with MCI present a deficits in visual-spatial functioning, even when these are not related to motor disability [84]. Other authors suggested that it might be the result of the hard cognitive involvement required by this kind of tasks [83]. Gray Williams [5] described two distinct cognitive impairment profiles of PD patients, associated with different neuropathological basis and clinical outcome. Executive deficits seem to be more common in the early stages of the disease, whereas posterior deficits seem to cover a greater role in the later stages of the disease. Posterior deficits are also considered important dementia predictors.

Neuropsychological Evaluation of PD Subjects without Dementia

Currently, there are no uniform guidelines for the neuropsychological assessment of PD patients with MCI. In 2010, Dalrymple-Alford [85] pointed out the variability of diagnostic criteria present in scientific literature. For example, several studies [18,86-88] identify as having MCI PD patients getting a score of at least -1.5 standard deviation (SD) in at least one administered test. Other psychometric criteria [40,85,89] indicate scores from -1.5 to -2.0 SD to make diagnosis. By contrast, some authors [90,91] require an average score *per domain* below -1.5 SD. Dalrymple-Alford [85] considered as necessary the presence of a -1 SD score and at least another score at -1.5 SD below normal to make diagnosis. Otherwise, the author request in the scales for the staging of dementia a score of 0.5, or lastly, the presence of individual complaints about one's condition [4,5,18,20,86,92]. Finally, some clinicians based their diagnoses on the clinical judgment [93-95]. Another issue on which scientific literature shows disagreement, is the amount of measurements that are necessary to state the presence of a cognitive deficit for each domain. Muslimovic [96] considered as non-demented patients whose scores are below -2 SD in two measurements. Other authors [12,97] just in one measurement. However, the utilisation of only one measurement might cause many normal subjects to be considered as MCI [98]. According to Dalrymple-Alford [85], the right compromise could be the use of one measurement for at least two cognitive domains. Furthermore, no uniformed guidelines have been outlined with regards to the use of tests required to make diagnoses. Although Mini-Mental State Examination (MMSE) [99] is one of the most used tests for the screening of patients in case of suspected dementia, its use on patients with Parkinson's disease is controversial in scientific literature [100,101], especially because of its low sensitivity in the identification of MCI (ceiling effect). According to Mamikonyan [40], MCI affects one third of the patients with Parkinson's disease that get a score in the range of normality in MMSE. Dalrymple-Alford in his study [85] tried to identify the diagnostic accuracy of Montreal Cognitive Assessment (MoCA), a screening test widely used in clinical settings and not specifically designed to diagnose PD. The study confirmed the external validity of MoCA and its effectiveness in discriminating between PD, PD patient with MCI and PDD. These capabilities would turn out to be better than those of MMSE. Hu [102] confirmed this result and reported how diagnosis made with the use of MMSE do not show temporal stability in longitudinal studies. Another study described the better validity achieved by MoCA than that obtained by instruments specifically designed for Parkinson's disease [103], such as the SCOPA-COG [18,86,101], or the PDD-Short Screen [104]. However, previous studies did not provide clear information on such a comparison [18,86, 101], probably because of less strict inclusion criteria for PD subjects with MCI. Further, Hoops [18] reported how MoCA shows an acceptable sensitivity (0.83) but a scarce specificity (0.53) in identifying PD subjects with MCI by means of 26/27. Currently, there are other largely used neuropsychological battery of tests for the assessment of deficits in patients with Parkinson's disease, such as the Mini Mental Parkinson Disease, [105], and the already mentioned SCOPA-COG [105].

The SCOPA-COG is an instrument that proves valid and sensitive for the measurement of cognitive dysfunctions of Parkinson's disease [106], but not exhaustive enough in the evaluation of cortical functions. Isella's study [107] too, in 2013, approved the use of SCOPA-Cog as screening tool for non-demented PD subjects' condition. Parkinson's Disease-Cognitive Rating Scale (PD-CRS) [108] is another available instrument capable of evaluating a wide range of cognitive functions, which proved valid and reliable in diagnosing Parkinson's disease. According to Pagonabarraga [93], this scale allows to identify the slight executive dysfunctions present in non-demented PD subjects. Several other global cognitive scales have been proposed as screening test for non-demented PD subjects, such as Parkinson Neuropsychometric Dementia Assessment (PANDA) [108], and Mattis Dementia rating scale (Mattis DRS) [109]. The last one, in particular, shows a sensitivity of 72% and a specificity of 86% in diagnosing PD subjects, with a cut-off of 130. Karrasch [110] claimed that the CERAD (Consortium to Establish a Registry for Alzheimer's Disease) neurocognitive test battery too, initially used for Alzheimer's disease, can be also be used as screening test for PD subjects. Lastly, the "Parkinson Disease Cognitive Functional Rating Scale" (PD-CFRS) [93], represents an instrument capable of measuring the impact of cognitive impairment on instrumental activities of daily living. Kulisevsky's [111] validation proves how adequate this instrument can be in the evaluation of PD subjects with MCI activities of daily living.

The Diagnosis and the Neuropsychological Assessment of PD-MCI

Many studies suggest that cognitive impairment in PD subjects may represent the earliest stage of PDD, as mentioned above. This is the reason why scientific literature tried to recognise its frequency and clinical characteristics and the best predictors of conversion from PD-MCI to PDD. A classic study of Lieberman [112] demonstrated how the incidence of dementia in Parkinson's disease (PD) was tenfold higher than among controls. According to this study, dementia was more related to the presence itself of PD than to the older age. In fact, several authors have shown how dementia is common in Parkinson's disease (PD). According to epidemiological data, between 24% and 31% of PD subjects meet criteria for dementia [6,113]. More specifically, longitudinal cohort studies have shown that between 20% and 60% of patients with PD develop dementia within 5 years [3,7,8,20,48,114-116]. Janvin [20] found that within the 62% of PD subjects with MCI converted to PDD over a 4-year period, patients with multiple domain MCI were the most frequent subtype. In other words, the frequency of conversion to PDD over a 4-year period was higher for the multiple domain MCI (63%) when compared to the non-amnestic single domain MCI (69%) or to the amnestic single domain MCI (40%). However, these studies utilised different definitions for PD-MCI, different populations and different neuropsychological tests. This heterogeneity prevents clinicians, patients, caregivers, and researchers to communicate appropriately and to improve patient care by the identification of patients at increased risk of developing PDD. Rapid identification allows early therapeutic interventions. Because of all these, in 2011, the International Parkinson and Movement Disorder Society (MDS) instituted a Task Force to critically evaluate literature and estimate the frequency and the characteristics of Parkinson's disease-Mild Cognitive Impairment and to supply its formal diagnostic criteria. "*PD-MCI*" was the nosographic label chosen by the MDS to define such a clinical entity, because of its frequent utilization in the literature [4,6,17,25,117,118]. These criteria would provide the first step in a uniform definition of PD-MCI (see Table **1**). One year later, Litvan and colleagues [21] proposed the diagnostic criteria for PD-MCI. The inclusion criteria required a diagnosis of Parkinson's disease based on the UK PD Brain Bank Criteria [119]; the presence of a gradual decline reported by either the patient or informant, or observed by the clinician; the verification of the cognitive deficits by either formal neuropsychological testing or by a scale of global cognitive abilities; and the presence of cognitive deficits not sufficiently severe to interfere with functional independence. The existence of a diagnosis of PD dementia based on MDS Task Force proposed criteria [120], of other primary explanations for cognitive impairment (e.g., delirium, stroke, major depression, metabolic abnormalities, adverse effects of medication, or head trauma) or of other PD-associated comorbid conditions (e.g., motor impairment or severe anxiety, depression, excessive daytime sleepiness, or psychosis) that significantly influence cognitive testing represented the exclusion criteria. PD-MCI diagnostic criteria provides for two levels of diagnosis in base of assessment availability. Level I diagnosis contemplates an abbreviated assessment and provides an inferior diagnostic accuracy. For Level I diagnosis, an impairment on a scale of global cognitive abilities validated for the use in PD must be present. Indications for the most adequate instruments were given. Otherwise,

when a limited battery of neuropsychological tests is performed, the impairment on at least two tests must be present to make diagnosis. In a similar way to PDD MDS criteria, five cognitive domains are considered: attention, working memory, executive functions, language, memory and visual-spatial ability. Level II represents a comprehensive assessment with a neuropsychological testing including two tests within each of the five cognitive domains cited. The impairment must be present on at least two neuropsychological tests (two impaired tests in one cognitive domain or one impaired test in two different cognitive domains) and demonstrated by a performance approximately 1 to 2 SDs below appropriate norms or a significant decline demonstrated on serial cognitive testing or from estimated premorbid levels [21]. Level II diagnosis is more sensitive than level I; it allows PD-MCI sub-domain categorization. Subjects who show abnormalities on two tests within a single cognitive domain while in the other domains result unimpaired are classified as PD-MCI single-domain. Subject who show abnormalities on at least one test in two or more cognitive domains are classified as PD-MCI multiple-domain. In both cases, the criteria suggest to specify the domains damaged. This represents a difference from Petersen's criteria [14], in which clinicians can differentiate only between amnestic and non-amnestic. On the ground of previous studies, the diagnosis has been established based on the presence of just one abnormal test [85,121], showing how more strictly criteria decrease diagnosis' sensibility. Such decision is nowadays criticized [122]. Some influencing factors are taken into consideration in the diagnosis' procedure, such as the premorbid functioning. Premorbid level of functioning can be evaluated based on subject's demographic characteristics. Alternatively, it is possible to assess specific tests, such as the National Adult Reading Test (NART) and the Wechsler Test of Adult Reading (WTAR), tests appositely built for the estimation of premorbid level of functioning. Psychiatric comorbidities (mood disorders, apathy, psychosis, sleep behavior disorder) are frequent in PD subjects and if these disorders are present, the subject must be evaluated after psychiatric symptomatology's resolution. Moreover, the PD treatment can strongly influence cognitive performance. This is the reason why the assessment must be completed during "therapy on period" and drugs known to have an effect on cognition must be avoided. Finally, severe motor symptoms could invalidate the reliability of the results of the neuropsychological evaluation, too. Tests that minimize motor demand must be used and patients must be evaluated in their optimal motor state.

Table 1: MDS Criteria for the Diagnosis of PD-MCI

PD-MCI proposed diagnostic criteria
I. Inclusion criteria
• Diagnosis of Parkinson's disease based on the UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria
• A gradual decline, in the context of established PD, of subjects' cognitive abilities
• Formal neuropsychological testing must confirm cognitive deficits
• Cognitive deficits are not sufficient to interfere significantly with independence in functional abilities
II. Exclusion criteria
• Diagnosis of Parkinson's Disease Dementia based on Movement Disorder Society Criteria (Emre et al., 2007)
• Other relevant explanation for cognitive impairment (e.g. delirium, stroke, major depression, etc.)
• Other comorbidity that may influence performances on testing (e.g.motor impairment or psychiatric disturbances)
III. Guidelines for PD-MCI Level I and Level II categories
A. Level I
• An impairment on a scale of overall cognitive abilities or on at least two tests if a limited battery of neuropsychological tests is used
B. Level II
• A complete neuropsychological testing (i.e. two tests for each cognitive domain: attention and working memory, executive functioning, language, memory, visuospatial functioning)
• The impairment must be present on at least two neuropsychological tests (e.g. one impaired test in two different cognitive domains/ two impaired tests in one cognitive domain)
• The impairment is demonstrated by a performance approximately 1-2 *SD*s below apposite norms
IV. Subtype classification (It requires Level II diagnosis)
• PD-MCI single-domain: abnormalies on two tests within a single cognitive domain
• PD-MCI multiple-domain: abnormalies on at least one test in two or more cognitive domains

For further details, see Litvan *et al*., 2012

After publication of the MDS criteria, many studies proceeded to their validation. For example, by using Litvan's criteria al Level I, Pedersen [123] reported that PD-MCI baseline subjects were older, less educated and with a major disease duration. They received a minor score in the Unified Parkinson's Disease Rating Scale (UPDRS) and in the Mini Mental State Examination (MMSE), and received a major score in

the Hoehn and Yahr scale when compared to the controls. Additionally, 27% of subjects developed dementia during a 3-year period, despite the 0.7% of the controls. The same predictive force is shown by the presence of PD-MCI at the first follow-up, one year after the baseline. Interestingly, reconversion rate from PD-MCI to an undamaged state was very high: 21.6% for PD-MCI at baseline and 19.4% for PD-MCI during the first follow-up. Among patients who show PD-MCI at the baseline and during the first follow up, 45% develop dementia and only 9.1% reconverted to a cognitively normal condition. Between these groups, performance on Stroop Test, verbal memory tests and age represent the discriminant factors. According to the author, non-amnestic single domain was the most frequent subtype. Conversely, Broeders and colleagues [124] employed level II criteria. 35% of subjects evaluated presented PD-MCI at the baseline and 48.5% at the first follow-up three years later, while 9.3% has converted into dementia. After 5 years, 38.4% of patients converted into PD-MCI and 23.3% into PDD. In contrast to the previous study, the multiple-domain one represented the most frequent PD-MCI subtype: 65.1% at the baseline, 63.8% after three years and 42.9% after five years. Once again, Goldman [125] discussed the optimal cut-off scores of tests adopted to evaluate PD-MCI. The better results come from the employment of a cut-off score of -2 SD from the norms (sensibility: 85.4%; specificity 78.6%). With this cut-off, in the study 61.8% of patients were classified as PD-MCI. The cut-off of -1.5 SD obtains a better sensibility (93.8%), but losing in specificity (60.7%). Multiple domain subtype results to be the most frequent one. Finally, by adopting the new MDS criteria, Marras [122] found that the percentage of subjects classified as PD-MCI consistently increases when the cognitive decline is evaluated on the basis of the premorbid level of functioning. This percentage reaches the 53% [20] in opposition to the 19%/25% of the previous investigation [4,6,17,18]. Noticeably, the evaluation starting from premorbid level of functioning results to be a strategy more sensible for identification of subjects at risk. Marras considered the cognitive performance declined when it falls at -1.5 SD from total IQ evaluation compared to previous level of functioning [122]. According to the author, 93% of subjects were classified as multiple domain PD-MCI. The percentage is higher than that reported in precedent studies, in which MDS criteria were not used. The reason for such results may be related to the MDS criteria request of just one abnormal test per domain to make PD-MCI multiple domain diagnosis. This is in contrast with the request of two abnormal tests for the diagnosis of PD-MCI single domain. When Marras changed Litvan's criteria, by defining multiple domains PD-MCI with two abnormal test *per domain*, the diagnosis distribution notably changed. In this case, the most frequent typology was the single domain. According to the author, the most represented sub-typology was the non-amnestic (executive and visual-spatial subtype). Other studies replicated similar results [4,20,126].

Table 2: Example of Global Cognitive Abilities Assessment and Premorbid Intelligence Estimation

Assessment	Neuropsychological Tests
Global cognition	Montreal Cognitive Assessment
	Parkinson's Disease-Cognitive Rating scale
Estimated premorbid intelligence	Wechsler Test of Adult Reading

For further details, see Litvan *et al*., 2012

Table 3: Examples of Tests for each Cognitive Domain

Cognitive Domain	Neuropsychological Tests
Attention and working memory	Trail Making Test Digit span backward
Executive function	Wisconsin Card Sorting Test Tower of London
Language	WAIS-IV Similarities Boston Naming Test
Memory	Rey's Auditory Verbal Learning Test Wechsler Memory Scale-IV
Visuospatial function	Benton's Judgment of Line Orientation Hooper Visual Organization Test

For further details, see Litvan *et al*., 2012

Neuropathological Findings

While in the mid-twentieth century primary studies focalized on the principal cerebral structures involved (i.e. substantia nigra) and on dopamine's role [127], recent investigations have demonstrated the involvement of other neurotransmitter systems [128,129] and cerebral structures [130]. To date, any neurobiological marker is clearly associated to PD-MCI and to its subcategories [21]. In fact, none of the biomarkers examined below specifically refers to PD-MCI. The descriptions of available biomarkers (including CSF, blood, and neuroimaging) and neuropathological features are one of the most compelling research aims. Some genetic polymorphisms (e.g., COMT polymorphisms and BDNF Val66Met genotype) have been associated with cognitive deficits in PD [131]. Several CSF biomarkers, such as a decreased CSF β-amyloid

(Aβ) 1-42, have also been proposed [132]. This finding has been interpreted not as a specific Aβ plaque pathology, but to synaptic α-synuclein pathology [133]. Structural neuroimaging, including diffusion tensor imaging, has described white matter anomalies in non-demented PD patients (*ibidem*). Gray Williams [5] described two different cognitive profiles of PD patients, connected with different neuropathological features and a different prognosis. Frontostriatal deficits seem to be linked to a dopaminergic depletion and are influenced by genetic factors (i.e. gene polymorphism COMT) and drug therapy. Whereas more posterior deficits seem to be associated to the degeneration of cholinergic fibres related to these neuronal networks [134] and are indicated as predictors for dementia development. According to Beyer, [135], PD subjects with cognitive impairment had reduced grey matter in the prefrontal cortex and temporal lobes when compared to PD subjects cognitively unimpaired. Compared with PD subjects without MCI, PD subjects with cognitive impairment show, in an fMRI study, an under-recruitment in the right dorsal caudate nucleus and the bilateral anterior cingulate cortex when compared with patients with Parkinson's disease without MCI. Furthermore, SPECT signal in the right caudate was lower in PD subjects with MCI than in patients with Parkinson's disease without MCI. Finally, according to Ekman [136], when compared with controls, patients with Parkinson's disease had under-recruitment in bilateral striatal and frontal regions. Noh and colleagues [137] verified by MRI how PD-MCI, differently from PD subjects without MCI, present a volumetric reduction of grey matter in the medium-frontal and posterior cingulate cortex, in the right temporal pole and in the left precuneus. Grey matter volume loss was observed in the right hippocampus, right cuneus, and right precuneus in PD subjects without MCI when compared to controls. PD subjects with MCI had significantly reduced grey matter volume in the bilateral temporal and frontal areas when compared to controls. By comparing amnestic MCI and amnestic PD subjects with MCI, MRI studies show how, in the latter group, a reduction in the density of the right parietal cortex, of the precuneus bilaterally and of the left motor cortex is present. By contrast, a comparison between amnestic PD subjects with MCI and amnestic MCI, showed decreased density in the right temporal and anterior prefrontal areas [138]. Grey matter density was significantly minor in the precuneus and in the left prefrontal and primary motor areas in the PD subjects with amnestic MCI when compared to controls. Temporal area atrophy was correlated with memory decline in amnestic MCI subjects, but with posterior cingulate cortex atrophy in amnestic MCI subjects with PD. Summarising, to date any cortex region is indicated clearly as a marker for PD-MCI, but in scientific literature, the most abnormal areas reported are frontal and posterior cortex. Only few studies utilised MDS criteria for PD-MCI to identify eventually biomarkes associated with these conditions: functional brain responses of right fusiform gyrus and of medial prefrontal cortex showed an abnormal longitudinal response in PD-MCI but not in PD subjects without MCI [139]. Segura [140] reported by a MRI study, signs of atrophy in the parietal and temporal cortex of PD-MCI subjects when compared with controls. Future prospective and longitudinal research is needed to clearly define biomarkers (cerebrospinal fluid, blood, and neuroimaging) that also include neuro-pathological correlations. Additional studies should improve our understanding of PD-MCI neurobiology on how to set up appropriate therapeutic interventions. When operative disease-modifying therapies will be established, early diagnosis will become an essential instrument in the prevention of this illness.

Non-Pharmacological Treatment

At present, there are no sufficient data about PD-MCI therapeutic interventions to propose guidelines on rehabilitation. Studies are extremely limited but they suggest the employment of computerised rehabilitative programmes [141]. According to Backman [142] these kind of programmes are able to improve dopamine's release. In the Paris' study, [143] the experimental group (n. 28) received a four week cognitive treatment, using a multimedia software and paper-and-pencil tasks while the control group was administered "*voice therapy*", a behavioural intervention technique. The treatment consisted of three rehabilitation sessions *per week* (45 minutes for each session). In the experi-mental group, attention, memory, processing speed, executive visual-spatial and visual-constructive abilities improved from baseline. However, no amelioration of life quality and personal or instrumental autonomy were reported. A non-randomised study [144] suggested an exercise program of 6 months, apt to improve executive performance in PD patients. In another study, patients were subjected to 12 one hour sessions of cognitive rehabilitation. The sessions were twice a week for a total of six weeks. The cognitive rehabilita-tion consisted of paper-and-pencil exercises and multimedia tasks. As a result, patients obtained a significant improvement in phonologic verbal fluency, classification and logical reasoning and logical memory tests. These results were confirmed at the 6-month

follow-up. There were no UPDRS significant variations, but subjective minor difficulties in complex tasks were reported [141]. In Nombela's study, the author investigates cognitive training's efficacy on the cognitive symptom's alleviation and whether such changes might alter brain connectivity. The performance of 10 patients and 10 healthy controls was compared in a modified version of the Stroop Test. After six months of cognitive training, PD-MCI patients showed a significant improvement in contrasting interference. Moreover, the experimental group showed reduced cortical activation patterns. The authors propose that cognitive training may stimulate cerebral resources, by balancing the alterations of the inhibitory circuitry [145].

DISCUSSION

Adopting an historical point of view, few manuscripts accurately describe the neuropsychological profiles observed in PD patients. Currently, the American Psychiatric Association (APA) (2013) proposes that diagnostic criteria for "Major or Mild Neurocognitive Disorder (NCD) are *probably* due to Parkinson's Disease" when the disturbance occurs in the setting of established Parkinson's Disease and there is an insidious onset and a gradual progression of impairment [11]. By contrast, in major or mild NCD *possibly* due to Parkinson's disease, PD clearly precedes the onset of the neurocognitive disorder. With regards to this issue, we noticed that neurocognitive disorder sometimes may precede motor symptoms, with a typical neuropsychological profile mainly characterized by visuospatial, memory and specific executive deficits in planning, sensitivity to interference and selective attention [146]. Therefore, a neuropsychological assessment must be now considered necessary to avoid clinical risk in the diagnosis. A copious set of data regarding the occurrence, risk factors, clinical progression, diagnostic criteria's reliability, temporal changes in cognitive performances and identification of biomarkers of PD-MCI needs to be recruited. More studies need to be performed to clarify all these issues. We believe that future investigations integrating neuropsychological and neuroimaging data should focus on the possible link present between the clinical phenotype (akinetic-rigid *vs.* tremor-dominant) and the different neuropsychological profiles of PD-MCI patients. This, should be carried out in order to describe different pattern f dysfunction and in order to evaluate if the risk of developing dementia changes between these different groups [147]. We do also stress that diagnostic criteria proposed by MDS [21] urge clinicians and researchers to pay attention in typifying PD-MCI for research purpose, with the aim of improving clinical knowledge about evolution and prognosis of each sub-category. Moreover, impairment in neuropsychological functioning should be objectively demonstrated by the prevalent use of psychodiagnostic instruments shared, where possible, by the scientific community, with the goal of obtaining epidemiological data to be effectively compared. The MDS task force recommends the use of at least two tests in each cognitive domain for the diagnosis of PD-MCI (level II). In any case, any strict indication is given about what kind of tests to utilise, furnishing only some examples of tests used in PD for global cognitive abilities' and cognitive domains' evaluation (see Table **2** and Table **3**). Because of the length of PD-MCI assessment, the MDS Task Force anticipated how, thanks to future researches, the domains and numbers of tests necessary would be reduced. Differences in the estimation of PD-MCI prevalence have led Litvan et colleagues [21] to recommend a less rigid range of 1-2 *SD* below appropriate norms for diagnosis, by disconfirming Petersen's original criteria for MCI [14]. However, as we have seen, this point is not clearly defined yet. Currently, there are no sufficient data about therapeutic interventions for PD-MCI to propose guidelines on cognitive rehabilitation. The effect of elective pharmacological treatment (e.g. levodopa) is mainly limited to motor symptoms and it can be associated to psychiatric therapy if patients present depression, apathy or sleep disturbances. As for non-pharmacological interventions, some authors suggest the employment of computerized rehabilitative programs while others propose/advocate prevention of cognitive deterioration by a multimodal rehabilitation that combines motor and cognitive training and support caregivers by instructing them [148]. Such strategy has shown its efficacy especially for executive functioning improvement: patients with MCI benefit more from cognitive training than patients with dementia, with positive implication for personal autonomy and quality of life. We believe that PD-MCI is a speedily developing area of investigation, with huge potential for the future.

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Received on 05-11-2014 Accepted on 17-12-2014 Published on 31-12-2014

DOI: http://dx.doi.org/10.12974/2309-6128.2014.02.02.5