Mild cognitive impairment and cognitive reserve in Parkinson’s disease

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ABSTRACT

Patients with Parkinson’s disease (PD) typically present with motor symptoms, but non-motor symptoms, including cognitive impairment, autonomic dysfunction and neuropsychiatric symptoms, are usually also present, when looked for carefully. The objective of this paper is to provide an up-to-date, comprehensive review of two undecided issues about cognitive impairment in PD patients without dementia: the concept of Mild Cognitive Impairment (MCI) and the concept of Cognitive Reserve (CR). Empirical findings support the value of the concept of MCI in this population, from the early untreated stages onwards. Further studies are needed to establish 1) the clinical-neuroimaging characteristics of MCI subtypes in PD, in comparison to those MCI subtypes in patients without PD; 2) whether different types of MCI in PD are associated with different rates of cognitive decline during the progression of the disease. Preliminary empirical evidence also shows that education might exert a protective effect on cognitive decline in PD and that less educated subjects are at increased risk for developing dementia, lending support to the CR hypothesis, in this population as well. Further studies are necessary to investigate how CR modulates cognitive decline in PD and other frontal-subcortical disorders, e.g. by identifying possible differential effects of CR on different cognitive domains.

1. Introduction

Parkinson’s Disease (PD) is characterized by motor (bradykinesia, rigidity and resting tremors) and non-motor symptoms such as cognitive impairment, autonomic, affective and behavioral disturbances [1]. Cognitive impairments are reported even in drug-naïve, newly diagnosed PD patients [2] and in subjects in the early stages of PD [3], with deficits being most prominent in the domains of memory, executive and visuospatial functions. Recent prospective studies showed that up to 75–80% of PD patients may eventually develop dementia during the course of the disease, the risk factors for which include: akinetic-dominant phenotype, early presence of hallucinations and subtle cognitive deficits [4].

In this review we provide an update of current evidence on two undecided issues related to cognitive impairment in PD patients without dementia: 1) the concept of Mild Cognitive Impairment
2. Neuropathologic bases of cognitive dysfunction in PD

PD is primarily caused by loss of dopaminergic neurons in the nigrostriatal pathway, resulting in reduction of dopamine levels in the striatum. This dopamine depletion has an impact on the functioning of four frontostriatal networks involved in motor, cognitive, affective and motivational aspects of behavior [7–10]. Three of these circuits are of particular interest with regard to cognitive dysfunction in PD patients (Fig. 1): the “dorsolateral” circuit including the dorsolateral prefrontal cortex (DLPFC), the striatum (dorsolateral caudate nucleus), the globus pallidus (dorsomedial) and the thalamus; the “orbital” circuit including the orbitofrontal cortex (OFC), the striatum (ventromedial caudate nucleus), the globus pallidus (dorsomedial) and the thalamus; the “anterior cingulate” circuit including the anterior cingulate cortex (ACC), the striatum (ventromedial caudate nucleus, ventral putamen), nucleus accumbens, the olfactory tubercle, the globus pallidus (rostromedial) and the thalamus. Within each circuit, two loops connect the striatum with the prefrontal cortex (PFC): a direct excitatory loop and an indirect inhibitory loop [8].

Executive functions are a set of processes necessary for appropriate, contextual goal-directed behavior, which allow a subject to: formulate goals with regard to their consequences, generate multiple response alternatives, choose and initiate appropriate actions, self-monitor the adequacy and correctness of these actions, to correct and modify them when conditions change and finally to persist in the face of distractions [11].

The prefrontal impairment, usually defined as a dysexecutive syndrome (including impairment in complex attention and executive functions) [12], that affects most PD patients from the early stages of the disease, is not directly due to the neuropathology of PFC, but to reduced dopaminergic stimulation at the striatal level, that disrupts the normal functioning of frontostriatal circuits. Anatomical and neuropathological evidence suggests that the evolving pattern of executive impairment in PD might be explained based on the spatiotemporal progression of dopamine depletion within the striatum, and its relation to the terminal distribution of its cortical afferents [10]. In the early stages of PD dopamine depletion is greatest in the foremost dorsolateral area of the head of the caudate nucleus, an area involved in the “dorsolateral” frontostriatal circuit. Executive functions related to this frontostriatal circuit are usually impaired from the early stages of PD and include functions of attentional control such as working memory, planning and task or set-shifting. In the early stages of PD, the orbital frontostriatal circuit and the related executive functions, that provide a reward-based control of behavior and the management of risk [13,14], are mostly preserved [15]. With the progression of disease, dopamine depletion affects also the orbital frontostriatal circuit, resulting in an impairment of related executive functions [10]. The temporal and spatial asymmetries of dopamine depletion and their relationship to cognition during the progression of PD-related neuropathology determine the differential effects of dopaminergic medication on cognitive functions in PD without dementia.

3. The clinical neuropsychology of Parkinson’s disease

3.1. Parkinson’s disease as a frontal-subcortical disorder

Cognitive deficits in PD were previously classified as one of the “subcortical dementias”, a heterogeneous group of disorders with primary pathology in subcortical structures and a characteristic pattern of neuropsychological impairment [16]. These disorders include Progressive Supranuclear Palsy, Corticobasal Degeneration, Huntington’s Chorea, and Vascular Dementia. These “subcortical dementias were contrasted with those of “cortical dementias”, such as Alzheimer Disease and Frontotemporal Dementia. Subsequently, the concept of “subcortical dementia” was abandoned, replaced by the term “frontal-subcortical dementia” [17], since anatomical and functional neuroimaging data showed that frontal deficits (i.e. the dysexecutive syndrome) result from a disconnection or a hypostimulation of the PFC from the basal ganglia [17,18]. In addition, most frontostriatal dementias, such as PD with dementia [19], show cortical atrophy in the later stages, and cortical dementias have subcortical pathology at some point. Hence, this distinction is somewhat artificial [17,18]; as a matter of fact, frontal-subcortical and cortical dementias describe the primary target of the disease process, and it is only in their initial stages that clear neuropsychological differences exist between them; in later stages, they result in a global dementia and neuropsychological profiles are almost indistinguishable [20].
3.2. The concept of mild cognitive impairment in Parkinson’s disease

The majority of studies on cognitive dysfunction in PD have included patients already taking dopaminergic medications. Few studies assessed cognitive functioning in newly diagnosed, untreated (de novo) PD [21–28], with the majority of studies reporting a mild cognitive dysfunction, with a prevalence varying from 18% to 36% (See Table 1). These different figures are probably due to the different numbers of cognitive tasks employed and to the criteria used to establish the presence of a cognitive dysfunction; in fact a preserved cognitive status of de novo PD was only reported by the study that used the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), rather than different tasks for each cognitive domain [28]. The term Mild Cognitive Impairment (MCI) defines the presence of cognitive deficits not severe enough to warrant the diagnosis of dementia; diagnostic criteria include: the presence of cognitive concern, of cognitive impairment in 1 or more domains as assessed with a neuropsychological examination, of normal functional activities and the absence of dementia [29]; individuals with MCI have an increased risk of developing dementia, with an annual conversion rate between 6% and 15% [29].

As expected, the cut-offs used to define impairment and the definition of MCI used, influence the prevalence of MCI: per definition, 15.9% of a normal population will score below 1 Standard Deviation of the mean on a single task, compared to only 2.3% using 2 Standard Deviation as a cut-off.

Studies with de novo PD patients showed that from the early, untreated stages of PD, they have an increased risk of developing an MCI compared to controls. In this stage of PD the increased risk of MCI is probably related to the dopaminergic dysmodulation, considering that patients do not show obvious cortical atrophy; a recent study found no correlations between cognitive performance and gray matter loss [30].

Different subtypes of MCI may be identified including those in patients with an isolated episodic memory dysfunction (for example in word-list recall tasks), patients with an isolated executive dysfunction (for example in tasks of working memory, verbal fluency, planning and cognitive control), or patients with a multi-domain MCI (memory, executive functions and/or language). These studies also revealed that, whereas amnestic MCI is the most common MCI subtype in the general population, non-amnestic MCI is the more common in de novo PD patients. Further studies are needed to establish if and how different MCI subtypes evolve differently into cognitive impairment during the course of PD, as the association between the cognitive profile of early PD patients and the subsequent risk of developing dementia is not well established [31].

With the progression of PD, patients develop impairments in several cognitive functions, which are not reviewed in this paper because other recent reviews are available covering prefrontal functions [32,33], language [34], visuospatial functions [35] and praxis [36]. Studies assessing cognition in treated patients at different stages of PD, show that 40%–50% of patients have cognitive dysfunction [37–40]. Classical screening tools for the evaluation of general cognitive status (for example the Mini Mental State Examination) may not be sensitive enough to detect cognitive difficulties in PD patients, which may result in under-recognition [41]. As a consequence, specific screening tools for PD (Mini-Mental Parkinson, Scales for Outcomes of Parkinson’s disease-Cognition, Parkinson’s disease Cognitive Rating Scale, Parkinson Neuropsychometric Dementia Assessment, Montreal Cognitive Assessment) or for executive functions [42–45] have been developed and require further research to establish accurate cut-off scores for the diagnosis of dementia and to identify cognitive deficits compatible with a diagnosis of MCI.

Even though the general pattern of cognitive impairment can be described as frontal-subcortical, studies in treated PD patients also described different types of MCI, including single-domain MCI (amnestic, executive or visuospatial impairment) or multi-domain MCI (impairment in more than one cognitive functions) [46–50]; hence, as for de novo PD patients, the concept of MCI is useful to describe the pattern of cognitive deficits in non-demented treated PD patients.

In treated PD patients, as in de novo PD patients, there is a higher prevalence of dysexecutive MCI [46–50]. Dysexecutive MCI has been related to frontostriatal dysfunction in PD patients [4,10] while it has been related to left PFC atrophy in patients without PD [51].

Memory impairment also appears as a primary feature in PD patients, and has been reported in de novo as well as early stage PD patients, in the absence of other cognitive dysfunctions [48]. Memory impairments in PD patients are heterogeneous: the retrieval deficit hypothesis, which suggests that PD patients may have more deficits in retrieval processes than in encoding processes [52] has been challenged in recent studies demonstrating the existence of different memory profiles [53–56]; overall, these recent findings argue against the sole presence of a retrieval deficit in PD patients, suggesting that encoding may also be impaired in this population. Further longitudinal studies are needed to establish whether different memory profiles in the amnestic MCI (impaired encoding, impaired retrieval, or both impaired) are

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample (n)</th>
<th>MCI%</th>
<th>Cognitive profile in the MCI-PD sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foltynie et al. [21]</td>
<td>159 (84 de novo + 75 early treated)</td>
<td>31.4%</td>
<td>33.7% dysexecutive MCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>23.8% amnestic MCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>57.5% multi-domain MCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>multi-domain MCI</td>
</tr>
<tr>
<td>Dujardin et al. [22]</td>
<td>44</td>
<td>36%</td>
<td>multi-domain MCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>multi-domain MCI</td>
</tr>
<tr>
<td>Muslimovic et al. [23]</td>
<td>115 (37 de novo + 78 early treated)</td>
<td>24%</td>
<td>multi-domain MCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>multi-domain MCI</td>
</tr>
<tr>
<td>Aarsland et al. [2]</td>
<td>196</td>
<td>18.9%</td>
<td>62.2% non-amnestic single-domain MCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.7% non-amnestic multi-domain MCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>24.3% amnestic single-domain MCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10.8% amnestic multi-domain MCI</td>
</tr>
<tr>
<td>Elgh et al. [25]</td>
<td>88</td>
<td>30%</td>
<td>46.6% single-domain MCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>53.4% multi-domain MCI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lower performance in tasks of executive functions and memory compared to HC Pathological MMSE score</td>
</tr>
<tr>
<td>Martin et al. [26]</td>
<td>26</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Kandiah et al. [100]</td>
<td>106</td>
<td>31%</td>
<td>Pathological MMSE score</td>
</tr>
<tr>
<td>Aarsland et al. [27]</td>
<td>56</td>
<td>18.9%</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Table 1

Studies describing MCI in de novo PD patients.
associated with different rates of cognitive decline. Amnestic MCI has been linked to cortical atrophy in the posterior cingulate area and in the precuneus in PD patients and to cortical atrophy in the temporal area in patients without PD [57]. Moreover, PD patients with amnestic MCI also present with subtle executive impairments in comparison to healthy controls [58], suggesting that executive dysfunction is always present in PD with MCI, even in the amnestic type, caused by the frontostriatal dysfunction.

As regards the multi-domain MCI, in PD patients it has been linked to a widespread hypometabolism involving parieto-occipital cortices [59,60]; however no studies with Magnetic Resonance Imaging have investigated patients that present this type of MCI but do not have PD. In summary, amnestic MCI and dysexecutive MCI may have different neuropathological bases in patients with PD as compared to patients without PD: further studies are needed to clarify the differences between the clinical-neuroimaging characteristics of similar MCI types in patients with and without PD.

A potential use of the concept of MCI in patients with PD is to predict different rates of conversion to dementia. Although in the early stages of PD cognitive decline progression is slow [61], close to 75% of patients surviving for more than 10 years develop dementia, the mean time from onset of motor symptoms to dementia being approximately 10 years [62,63]. Longitudinal studies that attempted to identify cognitive predictors of dementia failed to demonstrate homogeneous findings [31,59,64–70] (See Tables 2 and 3). The most common cognitive predictor was a deficit in executive functions; in particular in semantic fluency (for example asking the patients to generate as many names of colors, animals and fruits as possible within 1 min for each category) was the most common predictor, identified in 5 studies. In particular, semantic fluency performance was identified as a predictor of dementia in a series of studies that assessed the same cohort of PD patients 3 years [69] and 5 years [70] after the baseline assessment. Semantic and phonemic fluency (for example asking the patients to generate as many names beginning with f, a, and s as possible in 1 min for each letter) are equally impaired in PD patients [71], but a recent study found that only performance in semantic fluency tasks was related to atrophy in the temporal, prefrontal and cerebellar areas in PD patients [72]. An early deficit in semantic fluency could suggest that the pathology involves not only frontostriatal circuits, but also other cortical areas such as the temporal cortex: this could explain why this subgroup of patients present with a more marked and rapid cognitive deterioration.

Another important issue is the relationship between MCI and motor subtypes of PD. Jankovic [73] adopted the Unified Parkinson’s Disease Rating Scale (UPDRS) [74] to classify PD patients on the basis of the predominant motor symptoms. The subgroup characterized by postural instability and gait difficulty (PIGD-PD subtype) was cognitively more impaired in comparison to the subgroup characterized by tremor (Tremor-PD subtype). Subsequent studies showed that the PIGD-PD subtype is associated with a higher risk of developing dementia [75] and that patients whose PD is initially characterized by tremor frequently converted to a PIGD subtype before developing dementia [76]. In addition to the definition of PIGD-PD subtype on the basis of the UPDRS score, other studies confirmed that PD patients, whose predominant presentation is not tremor, present with increased levels of depressive features, cognitive impairment [50,64,77–79] and an increased risk of dementia [4]. In contrast two studies reported somewhat different findings: a study describing PD patients on the basis of motor symptoms and the side of motor onset, reported that PIGD-PD patients (independently from the side of onset) and patients with left-side tremor onset presented with cognitive impairment, while patients with right-side tremor onset remained cognitively preserved [80]. Another study suggested that patients with the PIGD subtype versus Tremor subtype may not present with different levels of cognitive impairment, but each motor subtype may be associated with different cognitive profiles [81]: the PIGD subtype was associated with an impairment in psychomotor speed and cognitive flexibility while the Tremor subtype was associated with an impairment in verbal learning and visuospatial perception.

In summary, even when studies adopted different methodologies and terminologies to distinguish PD motor subtypes, the majority of these studies suggested that patients whose clinical picture is characterized by the PIGD-PD subtype; akinetic-dominant subtype are at an increased risk for MCI. Postural instability and gait difficulty in PD patients do not respond well to dopaminergic drugs in comparison to other motor symptoms, suggesting that they may not be due to nigrostriatal dopaminergic denervation [82,83], rather more likely to be due to pathology in extra-nigral sites, including the pedunculopontine nucleus and neocortex [84]. A recent study, however, showed that the

### Table 2

Baseline demographic and clinical characteristics of patients in longitudinal studies on cognition in Parkinson’s disease.

<table>
<thead>
<tr>
<th>Study</th>
<th>PD subjects (baseline)</th>
<th>Follow up (years)</th>
<th>% of dementia at follow-up</th>
<th>Baseline age (years) Mean (sd)</th>
<th>Education (years) Mean (sd)</th>
<th>Duration of PD (years) Mean (sd)</th>
<th>UPDRS III Mean (sd)</th>
<th>H&amp;Y stage Mean (sd)</th>
<th>LEDD (mg) Mean (sd)</th>
<th>MMSE Mean (sd)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mahieux et al. [101]</td>
<td>89</td>
<td>3.5</td>
<td>30</td>
<td>72.2 ± 8.2</td>
<td>12.0 ± 4.7</td>
<td>7.9 ± 6.3</td>
<td>201.1 ± 9.5</td>
<td>1.95 ± 0.62</td>
<td>326.7 ± 323.5</td>
<td>27.5 ± 2.7</td>
</tr>
<tr>
<td>Levy et al. [65]</td>
<td>164</td>
<td>3.6</td>
<td>27</td>
<td>65.4 ± 10.0</td>
<td>11.1 ± 4.3</td>
<td>8.4 ± 6.6</td>
<td>16.5 ± 4.9</td>
<td>1.73 ± 1.28</td>
<td>364.2 ± 373.6</td>
<td>28.8 ± 1.3</td>
</tr>
<tr>
<td>Azuma et al. [66]</td>
<td>69</td>
<td>2</td>
<td>17</td>
<td>74.6 ± 8.2</td>
<td>9.4 ± 4.6</td>
<td>7.3 ± 5.8</td>
<td>32.0 ± 13.6</td>
<td>n.a.</td>
<td>n.a.</td>
<td>36.8 ± 14.1</td>
</tr>
<tr>
<td>Woods et al. [67]</td>
<td>36</td>
<td>1</td>
<td>n.a.</td>
<td>69.5 ± 10.7</td>
<td>11.8 ± 4.7</td>
<td>5.9 ± 7.2</td>
<td>22.2 ± 11.4</td>
<td>n.a.</td>
<td>n.a.</td>
<td>28.8 ± 1.3</td>
</tr>
<tr>
<td>Janvin et al. [68]</td>
<td>76</td>
<td>4</td>
<td>42</td>
<td>70.3 ± 5.8</td>
<td>14.8 ± 2.8</td>
<td>5.1 ± 3.8</td>
<td>25.1 ± 12.3</td>
<td>n.a.</td>
<td>n.a.</td>
<td>28.0 ± 1.4</td>
</tr>
<tr>
<td>Janvin et al. [31]</td>
<td>72</td>
<td>4</td>
<td>33.3</td>
<td>69.4 ± 5.8</td>
<td>14.4 ± 2.5</td>
<td>5.5 ± 3.3</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>29.1 ± 1.0</td>
</tr>
<tr>
<td>Williams-Gray et al. [69]</td>
<td>126</td>
<td>3.5</td>
<td>10</td>
<td>72.5 ± 6.0</td>
<td>9.8 ± 4.2</td>
<td>11.7 ± 4.0</td>
<td>2.8 ± 0.6</td>
<td>n.a.</td>
<td>n.a.</td>
<td>27.8 ± 2.4</td>
</tr>
<tr>
<td>Taylor et al. [64]</td>
<td>39</td>
<td>3</td>
<td>12.8</td>
<td>68.9 ± 9.8</td>
<td>9.3 ± 3.1</td>
<td>12.2 ± 4.9</td>
<td>2.3 ± 0.6</td>
<td>623.6 ± 259.9</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Williams-Gray et al. [70]</td>
<td>101</td>
<td>5</td>
<td>17</td>
<td>73.9 ± 6.9</td>
<td>8.9 ± 2.9</td>
<td>10.8 ± 4.0</td>
<td>2.7 ± 0.1</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

Legend: UPDRS — Unified Parkinson’s Disease Rating Scale; H&Y — Hoen & Yahr Stage; LEDD — Levodopa Equivalent Daily Dose; MMSE — Mini Mental State Examination; sd — standard deviation; n.a. — not available.
The dopaminergic system is also substantially affected from the early clinical stage in patients with the PIGD-PD subtype [85]. Hence, patients with a non-tremor motor subtype could have a more widespread neuropathology affecting not only the nigrostriatal dopaminergic system but also other systems. This could explain 1) why patients who present with a PIGD subtype at baseline are more at risk for subsequently developing dementia with progression of the disease; 2) the development of dementia frequently occurs when the Tremor subtype converts to a PIGD subtype.

3.3. The concept of cognitive reserve in Parkinson’s disease

Lower education levels were found to be associated with an increased risk of dementia in several cohort studies, suggesting that higher education may have a protective effect [86]. The CR hypothesis proposes a functional explanation of this observation, suggesting that more CI could be due to both innate factors and lifelong mental stimulation, resulting in a more efficient use of existing networks. “The CR model suggests that the brain actively attempts to cope with brain damage by using pre-existing cognitive processing approaches or by enlisting compensatory approaches. Individuals with more CR would be more successful at coping with the same amount of brain damage. Thus, the same amount of brain damage or pathology will have different effects on different people” [87; pp. 112]. The simplest explanation of how CR reduces the clinical effects of neurodegeneration is that CR allows some individuals to cope better with the consequences of pathology and remain clinically more intact for longer. Confirmation of this is provided by a large population-based cohort study [88], that demonstrated no protective effect, based on the number of years in education on the accumulation of neurodegenerative or vascular pathologies at death; education did, however, mitigate the association between burden of pathology and cognitive decline so that, for a specific level of pathological burden, those who had more education early in life were at a reduced risk for developing dementia in old age. Indirect confirmation is provided by another study [89], which found that memory decline accelerates many years before diagnosis during the preclinical stages of AD: educational achievement delays the onset of this accelerated decline, moving it closer to the time of dementia diagnosis; once it begins, the decline is more rapid in persons with more education, due to a more advanced stage of brain pathology.

Variables descriptive of lifetime experiences are commonly used as proxies for CR: these include measures of socioeconomic status, such as income or occupational attainment, educational levels and leisure activity [90]; however, the numbers of years of formal education is the most frequently adopted proxy in studies studying CR. Almost all CR studies were performed in samples of MCI patients who subsequently developed a “cortical dementia” like AD. On the basis of previous findings [88] and of our own clinical experience, we hypothesize that the CR hypothesis could also apply in a frontal-subcortical disorder like PD. This hypothesis, however does not have sufficient empirical support because of the limited number of studies investigating the relationship between cognitive function and education in PD patients. One study reported that a higher education level exerts no protective effect on the cognitive decline of PD patients, except in short-term memory [91], while another study found an association between higher educational levels and a lower risk of cognitive dysfunction [92]. With regard to the relationship between cognition, depression and education, one study reported that depression and executive functioning were only inversely related in PD patients with less than 5 years of formal education [93], while another study found a significant negative relationship between cognitive performance and severe depressive symptoms in PD patients with less than 12 years of formal education [94]. Finally, a recent meta-analysis of 25 longitudinal studies, involving 901 initially non-demented PD patients, showed that education significantly influences changes in the cognitive performance of PD patients over time [40]: fewer years of education were associated with a greater degree of cognitive decline in all domains and the influence of education was most pronounced on mental flexibility and reasoning, attention and processing speed, and memory [40].

In summary, these findings suggest that higher levels of education might exert a protective effect on cognitive decline in PD.
and that subjects with less education are more at risk for developing dementia, lending support to the CR hypothesis, in PD as well. Further studies, however, are necessary to investigate how CR modulates cognitive decline in PD and other frontal-subcortical disorders, e.g. by identifying possible differential effects of CR on different cognitive domains. The definition of high versus low education, based on the number of years of formal education, needs also to be standardized across the studies.

4. Conclusions: clinical implications

In this article we have reviewed recent studies on cognitive impairment in non-demented PD patients. The pattern of cognitive deficits in PD without dementia is compatible with the neurocognitive profile of frontal-subcortical disorders, caused by a neuropathology that primarily affects basal ganglia, reducing their dopaminergic input to the prefrontal cortex. Primary cognitive deficits, that may be present from the early symptomatic stages of PD, involve memory, executive and visuospatial functions.

The study of cognition in PD is of particular interest, because the spatiotemporal progression of dopamine depletion during the course of the disease provides a unique model for assessing dopaminergic effects on neural systems with differential baseline dopamine levels. The interaction between degrees of dopamine depletion (dorsolateral vs. orbital frontostriatal circuits; left hemisphere vs. right hemisphere) and dopamine replacement therapy produces different cognitive profiles at different stages of the disease. This complex clinical picture could partially explain why the findings of studies on cognitive functions of PD patients are heterogeneous [95]. Additional data are needed to determine how asymmetry in dopamine depletion interacts with neural correlates of cognitive functions in PD: the challenge lies in developing a theoretical model that can link evidence from pathophysiological and neuroimaging studies with clinical and neuropsychological findings. This model should explain how interactions between the clinical stages of PD and medication produce different patterns of cognitive impairment along the course of the disease.

On the basis of this review several questions can be raised and recommendations made to clinicians caring for PD patients. First, a neuropsychological evaluation is useful even in the early stages of PD, when patients may appear cognitively preserved: 20–30% of patients already present with subtle or mild cognitive impairments when adequately tested. The neuropsychological assessment should cover all cognitive domains, but in particular executive and visuospatial functions and episodic memory functions. In particular a baseline neuropsychological assessment is indicated for patients with PIGD-motor subtype and a low educational level as these constitute the main risk factors for the development of dementia. Follow-up is particularly important for those patients with an impaired baseline performance; those with a deficit in semantic verbal fluency should be followed more closely, as this constitutes a particular risk factor for dementia.

Finally, identification of MCI in PD patients, opens the debate on interventions for preventing dementia. Pharmacological interventions in amnestic MCI, considered the prodromal phase of AD, have produced negative findings with regard to reducing the conversion rate to dementia [96]. Cognitive training/rehabilitation programs in this population have shown only positive short-term effects on memory functions [97]. Such interventions have not yet been widely investigated in non-demented PD patients with MCI, preliminary beneficial short-term effects have been reported in some executive functions [98,99]. Clinical trials are needed to assess the efficacy of pharmacological interventions or cognitive rehabilitation programmes to delay cognitive worsening and conversion to dementia in PD patients.

Author roles

1. Research Project: A Conception B Organization C Execution
2. Manuscript: A Writing of the Draft B Review and Critique
   Poletti 1A 1B 1C 2A
   Emre: 2B
   Bonuccelli 1A 1B 2B

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Advisory Boards:
   Bonuccelli: GSK, Lundbeck, Novartis, UCB
   Emre: Merck; Serono, Novartis, Onon, Teva, Lundbeck, Boehringer Ingelheim

Partnerships: none

Honoraria:
   Bonuccelli for speeches at meeting by Boeringhehr, GSK, Novartis
   Emre: for speeches at meeting by Merck Serono, Novartis, Onon, Teva, Lundbeck, Boehringer Ingelheim

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Contracts: none

Royalties: none

Other: none

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