Neuropsychological Features of Early Cognitive Impairment in Parkinson’s Disease

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Abstract
Cognitive impairment can be evident even in the earliest stages of Parkinson’s disease (PD). Executive dysfunction due to disruption of dopaminergic frontostriatal circuitry is well recognised, but deficits also occur across other domains, including memory and visuospatial function, and these deficits may have a non-dopaminergic basis. There is growing interest in the concept of mild cognitive impairment in PD, which may have important prognostic implications in terms of predicting the development of dementia. Cognitive impairment in early PD is heterogeneous, and hence particular subtypes of mild cognitive impairment might have particular prognostic significance. This chapter will review the prevalence of neuropsychological deficits in early PD, and discuss whether these deficits have any functional impact on the day to day life of PD patients. We will then consider the most appropriate neuropsychological tools to use in early PD given the limitations of current instruments and difficulties in neuropsychological testing in this patient group. Longitudinal data exploring the evolution of early cognitive deficits over time and their relationship with later occurring dementia will then be discussed. Finally, we will review current knowledge about the underlying pathophysiology of cognitive impairment in early PD, which has important implications for better understanding the neurobiological basis of PD-associated dementia.

Cognitive deficits are detectable with neuropsychological testing from the earliest stages of Parkinson’s disease (PD) [1, 2]. They may be reported by the patient or carer, but in some instances are subclinical. There is growing interest in early cognitive impairment in PD, with the recent proposal of a diagnostic term for this aspect of the disease, namely PD-associated mild cognitive impairment (PD-MCI) [3], analogous to the MCI which is thought to be a precursor of Alzheimer’s disease [4]. Whilst these impairments may be problematic in their own right with a direct impact on the patient’s daily life, they may also have important prognostic value by identifying those patients who are likely to go on to develop dementia.
This chapter will review the frequency of early cognitive impairment in PD, discuss the profile of cognitive domains typically affected, and consider the behavioural consequences of these early cognitive deficits. We will then discuss the most appropriate neuropsychological tools to use in this population, an issue which remains under debate. A small number of longitudinal studies have attempted to explore the relationship between early cognitive deficits and later occurring dementia, and these prognostic data will be discussed. Finally, we will consider the underlying pathophysiology of early cognitive impairment in PD that has implications for understanding how dementia in PD evolves and for the development of future therapeutic strategies.

**Epidemiology**

A number of studies have investigated the prevalence of cognitive impairment in non-demented PD patients; most estimates are in the region of 20–40% [1–3, 5–7]. Even amongst those with normal Mini-Mental State Exam (MMSE) scores, 29% have detectable cognitive deficits, highlighting the need for detailed neuropsychological testing in early PD [7]. The prevalence of early cognitive impairment depends on a number of factors, including whether the cohort is incident (i.e. only includes newly diagnosed patients) or prevalent (includes all patients with the diagnosis, no matter when diagnosed), hospital or community based, the selection of neuropsychological tests employed, and the criteria used to define cognitive impairment. Large-scale, community-based incident cohorts with comprehensive neuropsychological test batteries would provide the most accurate estimates, but these are lacking.

The number of impaired tests required and the cut-off levels for impairment also have a major impact on estimated prevalence, as demonstrated in a recent study which assessed 20 neuropsychological measures across 4 cognitive domains in 119 non-demented PD patients [8]. This study reported that prevalence figures varied from 14% when using 2 scores in 1 domain at 2 standard deviations below normal, to 89% of patients (and 70% of healthy controls) when using 1 score from 1 domain at 1 standard deviation below normal. The authors suggest that 2 scores below 1.5 standard deviations from the normative mean, either within 1 domain (30% prevalence) or across 2 domains (37% prevalence) are the most suitable criteria to adopt.

The most reliable data on the prevalence of early cognitive impairment in PD come from a recent large multicentre analysis including 1,341 PD patients, which reported a frequency of 25.8% (CI 23.5–28.2) [9]. The authors adopted criteria similar to those proposed above, with 1.5 standard deviations below the normative mean taken as the cut-off for impairment and impairment within 1 domain being sufficient, with test scores averaged within each domain. However, only 3 cognitive domains were specified (attention/executive, memory, visuospatial), not all centres had data on all 3 domains, and in some centres, performance on a domain was determined on the basis of a single neuropsychological test.
Profile of Cognitive Deficits

Neuropsychological deficits in early PD occur across multiple domains including executive function, attention, memory and visuospatial function, but language deficits are less commonly reported.

Of the range of cognitive deficits described in PD, the most commonly described are impairments of executive function, i.e. planning, organizing and regulating goal-directed behaviour. These deficits are similar to those seen in patients with frontal lesions and are thought to represent a dysfunction of dopaminergic frontostriatal circuitry. They are demonstrated on neuropsychological tests sensitive to frontal lobe dysfunction, including planning tests based on the ‘Tower of London’ task and tests of spatial working memory [10, 11]. Deficits in sustained attention (e.g. in vigilance tasks) are reported only rarely in non-demented PD patients and have been interpreted as reflecting difficulties with executive control [12]. However, PD patients do tend to be impaired from an early stage in attentional set shifting, i.e. in altering behaviour according to changes in the relevance of stimuli [13]. This may reflect a degree of ‘cognitive rigidity’, i.e. the difficulty in disengaging from one task and engaging in a new task, particularly whilst still being distracted by a previously relevant dimension.

Impairment of explicit memory (a temporolimbic function) in early PD has been widely reported [1, 2, 5, 14]. Performance of PD patients in recall tasks is improved by semantic cueing or probing, unlike in Alzheimer’s disease, and PD patients are said to perform relatively better on recognition tests than free recall [15, 16]. These findings have led to the suggestion that the memory deficit in PD lies in retrieval rather than storage of information, possibly reflecting a deficiency in internally cued search strategies due to the dysexecutive syndrome [17]. In support of this hypothesis, it has been reported that memory performance test scores in patients with PD correlate with executive performance scores [16]. However, more recent work demonstrates that executive dysfunction and temporal lobe-based deficits can occur independently in PD [1]. Furthermore, memory impairment in PD seems to be more heterogeneous than originally thought, with some patients exhibiting problems with retrieval memory whilst others have deficits in encoding [18, 19].

Visuospatial and constructional deficits are a well-recognised component of the dementia of PD. They are less commonly reported in early PD but do seem to occur in some patients [2, 5, 14, 20]. Whilst such deficits are widely thought to reflect parietal lobe dysfunction [21], it has been suggested that impaired performance on visuospatial tasks in PD may be related to problems with sequential organization of behaviour [22]; in other words, may be at least partly attributable to frontal executive dysfunction rather than pure parietal pathology.

Language deficits are not commonly reported in PD, although there are isolated reports of deficits in sentence comprehension [23], naming ability [2] and language expression [14]. This apparent rarity of language dysfunction in PD may reflect the fact that this domain is often neglected in neuropsychological batteries.
Verbal fluency deficits, both semantic (category, e.g. animals) and phonemic (lexical, e.g. for letters FAS) are well reported in PD [24]. The appropriate neuropsychological domain within which fluency deficits belong is a matter of debate, as the tasks rely on executive search and retrieval strategies and psychomotor speed as well as semantic memory and language expression. A meta-analysis including 4,644 patients concluded that PD patients are more impaired on semantic fluency than phonemic fluency, and suggested that these deficits are particularly associated with semantic memory [24]. This pattern of verbal fluency dissociation is more akin to the cortical dementias, such as Alzheimer’s and semantic dementia [25], rather than the subcortical dementias, such as progressive supranuclear palsy [26] where phonemic fluency deficits predominate.

Whilst some authors have argued that seemingly disparate aspects of cognitive dysfunction in PD including memory impairment, visuospatial dysfunction and impaired verbal fluency are largely explained by the dysexecutive syndrome with a neuropathological substrate in frontostriatal circuits, it seems more likely that cognitive impairment in PD is heterogeneous. A population-based study of newly diagnosed PD patients (CamPAIGN) identified subgroups with differing patterns of cognitive impairment in the very early stages of the disease [1]. 142 patients were classified into 4 distinct groups: no cognitive impairment (n = 92); frontostriatal type impairment (n = 17); temporal lobe type impairment (n = 12) and global impairment (n = 21). Cluster analysis techniques have also been adopted to investigate heterogeneity of cognitive dysfunction in PD, reporting 3 separate subgroups, memory/attention, executive/motor and visuospatial [27]. Furthermore, studies attempting to define MCI in PD report impairment in single domains more commonly than multiple domains [3, 9]. The multiple aetiopathologies underlying the cognitive deficits in early PD will be discussed below.

**Neurobehavioural Correlates**

It remains unclear how much of an impact early cognitive deficits have on behaviour and day-to-day functioning in typical PD patients. Although a cross-sectional study of 124 non-demented PD patients has reported an independent association between neuropsychological test performance and health-related quality of life in a multivariate analysis, the cohort was not representative of idiopathic PD, with 64% of the patients being young onset (<50 years) [28]. Given that cognitive impairment in early PD is heterogeneous, one might anticipate that different deficits will have differing consequences in terms of their impact on activities of daily living (ADL). A small study of 39 idiopathic PD patients, exploring correlations between cognitive and motor function and ADL, found that executive deficits were associated with impairment in instrumental ADLs, e.g. shopping, preparing meals and handling finances, which require planning and organisation, whereas timed motor tasks were more associated
with physical ADLs, such as eating and dressing. However, their neuropsychological assessments were restricted to the trail making test and the digit ordering test, both assessing executive function [29]. A further study explored capacity to consent in 20 PD patients with cognitive impairment compared with 20 elderly controls [30]. The PD group were significantly impaired across all domains of a standardised competency measure, of which executive dysfunction was identified as the most important neuropsychological predictor.

Testing for Cognitive Deficits

There is no clear consensus about the best cognitive tools to use in early PD. This is likely to contribute to the heterogeneity of impairments reported in this field. Neuropsychological tests can be divided into global screening instruments, including those used across a range of disorders as well as those specific to PD, and tests which are designed to probe particular neuropsychological domains.

Global Screening Assessments

Global screening assessments can be useful to identify whether a patient is performing at a suboptimal cognitive level. They are commonly used in clinical practice, and are not designed for any particular disease. They include the MMSE [31], Addenbrooke’s Cognitive Exam-Revised (ACE-R) [32] and the Montreal Cognitive Assessment (MoCA) [33]. These tools assess multiple cognitive domains, with the ACE-R and MoCA providing individual domain scores. However, they have been criticised for their lack of sensitivity to detect deficits commonly reported in early PD and are not ideally suited to pinpoint the specific nature of any impairment. The MMSE, in particular, has never been systematically validated for use in PD, although it has been widely used in both clinical and research settings primarily because the scale is brief, and requires minimal training to administer. However, with a maximum score of 30, the MMSE is prone to floor effects in patients with severe cognitive impairment and ceiling effects for patients with MCI [34]. The MMSE also lacks sensitivity to cognitive dysfunction in PD. In particular, many scale items assess verbal memory and language, areas not thought to be dramatically affected in early PD, at the expense of measures of executive function, which is known to be impaired in a significant proportion of early PD patients. Furthermore, research has shown that a cut-off of ≤24 (which is used clinically to indicate dementia) shows a strikingly low sensitivity for the diagnosis of PDD [35].

In recent years, the MMSE has been used less frequently as other cognitive screening instruments have been validated for use in PD. One such scale is the MoCA. While still brief to administer, the MoCA includes more items assessing executive function, and has been shown to be sensitive to global cognitive impairment in both early PD (receiver operating characteristic area under the curve, ROC AUC: 87–91%) and later
Early Cognitive Impairment (ROC AUC: 78–90%). Although the specificity of this scale as a diagnostic measure is suboptimal, it far exceeds that of the MMSE [36]. Longer scales such as the ACE-R have used the MMSE as a starting point and expanded on it by incorporating small sections from other cognitive batteries such as Visual Object and Space Perception [37]. As a result, the ACE-R provides a more comprehensive summary of cognitive functioning in five domains: attention/orientation, memory, fluency (executive function), language and visuospatial. Although this test takes much longer to administer (approximately 25 min) than the MMSE, it has been used extensively in clinical practice [38]. The ACE-R has been validated against the Mattis dementia rating scale as a tool for evaluating dementia in a PD population [39]. Importantly, the ACE-R is also able to distinguish the cognitive profile of non-demented PD patients from other neurological conditions [McColgan and Williams-Gray, unpubl. data].

More recently, PD-specific scales have been developed such as the Scale for Outcomes of Parkinson’s Disease – cognition (SCOPA-cog) [40] and the Parkinson’s Disease-Cognitive Rating Scale (PD-CRS) [41]. The SCOPA-cog was originally designed as a tool for comparing groups of PD patients in a research setting [40], although it is now commonly used as a screening tool for PD dementia. Because the SCOPA-cog was created specifically for use in PD patients, it is weighted heavily for frontostriatal function. It has been successfully validated [40, 42] and shown to demonstrate better discriminative ability than the MMSE [40]; however, this was only true when comparing mild/moderate PD (Hoehn & Yahr = 2) to late PD (Hoehn & Yahr = 4/5), and it was relatively insensitive to the deficits experienced in very early PD [43]. The PD-CRS was designed to capture the full spectrum of cognitive deficits seen in PD and includes tasks which assess ‘instrumental-cortical’ functions and ‘frontal-subcortical’ functions. It reliably differentiates between cognitively intact PD patients and those with either PD-MCI or PDD as well as between those with PD-MCI and PDD. A cut-off score of ≤64 yields high sensitivity when screening for PDD [41], but no cut-off score has been reported for PD-MCI as yet.

Domain-Specific Neuropsychological Tests
Executive function refers to the mental processes necessary for the realization of goal-directed behaviour; these processes are thought to rely upon the functional integrity of the prefrontal cortex [44]. A wide array of tests have been used to assess executive dysfunction in early PD, including tests of planning such as the Tower of London [45] or Cambridge Neuropsychological Test Automated Battery (CANTAB) Stockings of Cambridge tests [46], tests of set-shifting behaviour such as the Wisconsin Card Sorting Test [47], and several variations of the verbal fluency tasks including tests of phonemic and semantic fluency [48]. Tests of attention measure the brain’s ability to filter relevant and irrelevant information in response to given criteria. The concept of ‘attention’ overlaps strongly with the executive function of ‘working memory.’ It is difficult to delineate tasks that only measure attention in the absence of working memory. In PD, attention is typically measured through standardised tests such as the
Stroop colour-word test, the digit span test (forward and backward) and the Reitan Trail-Making test (part A and B) [45].

Visuospatial function is typically assessed using figure copying or drawing tests, which are known to be impaired by parietal lobe lesions [21]. The pentagon copying task derived from the MMSE has been reported to have predictive value for later occurring dementia in PD [20]. The clock drawing task has also been widely used in PD; points are attributed for the accuracy of the drawing, in particular the inclusion of all necessary features and the appropriate spacing of the numbers [49]. Clock drawing performance probably relies on a range of neuropsychological functions including executive as well as visuospatial function, although a study of 133 patients with focal brain damage indicated that the strongest neuroanatomical correlates of clock drawing performance were predominantly in the parietal cortex [50].

In terms of assessing memory performance, word list learning tests with delayed recall and recognition conditions, such as Rey’s Auditory Verbal Learning Test, the California Verbal Learning Test and the Hopkins Verbal Learning Test [45] are preferable to prose recall tests which can be relatively unreliable. Tests of non-verbal memory in this population are problematic as most visual memory tasks rely on recognition memory which is less sensitive to early memory decline. The Brief Visuospatial Memory Test-Revised [51], however, allows for the assessment of any motor impairment which can then be considered when interpreting the data. Language is reported to be relatively preserved in PD patients with cognitive impairment [52], but confrontation naming tasks such as the Boston Naming test and the Graded Naming Test [53] are useful measures of language ability in early PD.

As with many other movement disorders, evaluating the cognitive profile accurately can be difficult in patients with PD. Cognitive tasks often rely on a degree of manual dexterity (e.g. clock drawing tasks), or need complex and prolonged motor responses (e.g. Rey Osterrieth Complex Figure), so that performance can be confounded by motor impairment in PD. The picture is further complicated by the use and timing of anti-PD medication, especially dopaminergic agents. Patients should therefore be assessed when ‘ON’.

Bradykinesia can disadvantage patients in timed tasks which require the patient to maximise performance within a given time frame, such as the Stroop test, or in tests of verbal fluency. Additionally, the subtle delay introduced by motor slowing to immediate recall tasks such as the initial stages of the Hopkins Verbal Learning Test and the Digit Span test can add an additional memory load that affects performance. In tests with reaction time, detailed measurement is needed to ensure that bradykinesia is not misinterpreted as cognitive slowing. Computerised test batteries, such as the CANTAB, try to address this by measuring components of reaction time, allowing the researcher to differentiate between motor (movement time) and cognitive (movement initiation time) slowing. The graded nature of most tasks in the battery reduces the probability of floor and ceiling effects. CANTAB has been widely used to evaluate executive function in early PD, with multiple studies reporting problems with planning, measured
by the Stockings of Cambridge [10] and One-Touch Stockings [54], and attentional set shifting, measured by the Intra-/Extradimensional Shift task [55].

Finally, depression and apathy, which are commonly reported in early PD, are both associated with increased cognitive impairment, particularly in the domain of executive function [56, 57]. These neuropsychiatric symptoms should ideally be screened by using appropriate tools, and caution should be exercised when interpreting the data from neuropsychological assessment in patients who exhibit these features.

At present, there is little consistency in the tests used to identify cognitive impairment in early PD. The choice is vast, and the research supporting the sensitivity and specificity of tests in this population is limited. Ultimately, cognitive batteries are designed based upon convention, preference and availability rather than scientific grounding. A more coherent approach to cognitive testing in PD is necessary and may help to reduce some of the heterogeneity currently reported.

Prognosis

MCI in PD is a risk factor for later dementia [58]. However, studies evaluating the prognosis of global MCI are likely to be too simplistic to yield meaningful results. There is considerable evidence that early cognitive impairment in PD is heterogeneous [1, 2, 9], and hence it is important to establish whether domain-specific impairments have particular prognostic value for dementia. Given the relatively recent emergence of the concept of MCI in PD, there is still a lack of longitudinal data exploring the relationship between MCI subtypes and dementia, although one small study has reported that amongst 59 patients followed up over 4 years, single-domain non-amnestic MCI and multiple-domain MCI were associated with later development of dementia, whereas amnestic MCI was not [58].

A number of previous longitudinal studies have investigated the relationship between performance in individual neuropsychological tests and later dementia with varied and inconsistent results: executive deficits [59–61], impaired verbal fluency [60, 62], visuospatial deficits [60] and memory and language dysfunction [61, 63] have all been suggested as useful prognostic markers. These findings are limited by the selection of neuropsychological tests employed, as well as by the nature of the cohorts studied: these cohorts included patients of widely varying disease duration, most collected from hospital settings not representative of the general population.

The CamPaIGN study has investigated how cognitive function evolves over time in a newly diagnosed PD cohort. The authors attempted to recruit all patients within Cambridgeshire, UK, over a 2-year period using multiple sources in hospitals and the community [1]. The resulting cohort of 122 patients underwent detailed neuropsychological testing and has been followed up longitudinally, with data at 3.5 and 5.2 years from diagnosis being published so far [20, 64]. Analyses at both time points have shown that two neuropsychological tests performed at baseline, namely
semantic fluency (<20 words in 90 s) and pentagon copying, are significant predictors of dementia, independent of age and other potential confounding factors. Suboptimal scores in these neuropsychological predictors plus age greater than 71 years resulted in an odds ratio of 8/11 versus 1/34 patients (OR: 88; 95% CI 8–962) for the development of dementia at 5.2 years. There was a dissociation between semantic and phonemic fluency, with the latter having no association with later occurring dementia. This implicates the more temporal lobe-based semantic memory system as the critical predictor, rather than frontally based search and retrieval strategies which are common to both fluency tasks. Hence, the best neuropsychological predictors of dementia in this study were ‘posterior cortical’, whilst there was no apparent association between ‘frontostriatal’ executive deficits and later occurring dementia. In fact, there was no clear deterioration in executive function over time. This work suggests that there may be at least two distinct cognitive syndromes in early PD which evolve differently: frontostriatal executive deficits which are common but do not necessarily worsen over time, and more posterior cortical deficits which herald decline to dementia (fig. 1). These cognitive syndromes appear to differ not only in terms of prognosis, but also in terms of their underlying pathophysiology, as discussed in the next section.

Other studies have provided additional support for the hypothesis that there is dissociation between early frontostriatal executive and posterior cortical cognitive syndromes [41, 65]. For example, a large meta-analysis of 25 longitudinal studies involving 901 PD patients has explored differences in the progression of impairment in multiple cognitive domains. Over a mean follow-up period of 29 months, significant cognitive decline occurred in global cognitive ability, and in the domains of visuospatial function and memory, but not in executive function [65].

A potential concern with all longitudinal studies to date is that they have used DSM-IV criteria to diagnose dementia, which are biased towards more posteriorly based cognitive deficits, in that memory impairment is an absolute requirement for the diagnosis in addition to impairment in one other cognitive domain. It could therefore be argued that the identification of posterior cortically based deficits as neuropsychological predictors of cognitive decline and dementia is simply a reflection of this diagnostic bias towards more posterior deficits. PD-specific dementia criteria have recently been proposed [52], which require impairment in any 2 cognitive domains (attention, executive, visuospatial, memory): they are likely to be adopted in future studies and will circumvent this argument. Diagnostic criteria for MCI in PD are also currently under development and should be helpful to ensure that future longitudinal studies adopt more consistent methods for examining and categorising early cognitive impairment in PD.

**Pathophysiology**

The majority of postmortem studies report that Lewy body deposition in limbic and cortical areas is the best correlate of dementia in PD [e.g. 66, 67], although Alzheimer’s
type neurofibrillary tangles and amyloid-β plaques also appear to contribute [66]. Postmortem studies examining MCI in PD are very limited for obvious reasons; one report has specifically examined the relationship between pathological findings at post-mortem and subtypes of MCI [68]. The authors studied 8 cases with parkinsonism: all went through a stage of MCI, 7 developed dementia prior to death, 6 had neocortical-predominant Lewy body disease and 2 had limbic-predominant Lewy body disease, with only 1 case having co-existing Alzheimer’s disease. They found no clear relationship between Lewy body pathology and subtype of MCI. The obvious disadvantage of such studies is that they cannot prospectively examine the evolution of cognitive deficits in the early stages of PD. Hence, alternative methods including genotype-phenotype correlation studies, structural and functional brain imaging, and pharmacological manipulation of neurochemical systems must be relied upon.

A number of candidate genes have been considered as potential factors influencing cognitive decline in PD. APOE, whose ε4 allele is strongly associated with Alzheimer’s disease, has been well studied in this respect, but a recent large meta-analysis including 4,198 PD cases and 10,066 controls did not support a clear association between APOE-ε4 and dementia, and longitudinal analysis of a subset of cases

Fig. 1. Schematic representation of hypothesised aetiological pathways leading to cognitive dysfunction in early PD and their relationship to the development of dementia 5 years later. The findings of the CamPaIGN study suggest that ‘frontal executive’ impairments in early PD are a consequence of a hyperdopaminergic state in the prefrontal cortex which is in turn modulated by COMT genotype and dopaminergic medication. These deficits were not associated with subsequent global cognitive decline and dementia over 5 years of follow-up. In contrast, it is proposed that early deficits on more posteriorly based cognitive tasks do not have a dopaminergic basis, but reflect Lewy body deposition in posterior cortical areas, which is in turn influenced by MAPT genotype and the ageing process. Reproduced with permission from Williams-Gray et al. [20].
revealed no association between this allele and rate of cognitive decline [69]. The α-synuclein gene is another obvious candidate, and studies of kindreds with autosomal dominant forms of PD carrying α-synuclein gene missense mutations or triplications reveal that these abnormalities in α-synuclein genotype are associated with early onset PD with dementia [70–73], but there has been no convincing evidence of a relationship between genetic variation in α-synuclein and early or late cognitive dysfunction in idiopathic PD. One gene which has proved more interesting however is the micro-tubule-associated protein tau (MAPT) gene. A common inversion polymorphism of chromosome 17 containing the MAPT gene (H1 versus H2 haplotype) is known to have a small effect on susceptibility to PD (OR 1.4, p = 2 × 10⁻¹⁹), but the CamPaIGN study has suggested that MAPT H1 variant has a much more profound effect on longitudinal cognitive decline in PD (fig. 2) [74]. The odds of developing dementia are reported to be 12 times greater in those carrying the H1/H1 genotype after correction for age [20], thus implicating the MAPT H1 variant as by far the most important genetic factor contributing to cognitive heterogeneity in PD reported to date. Furthermore, there is evidence that this variant has a functional impact, increasing transcription of 4-repeat tau in PD-affected brains [20]. These data implicate protein aggregation in the dementing process of PD, particularly when interpreted in the light of recent studies suggesting a synergistic interaction between α-synuclein and tau in Lewy body formation (fig. 1) [75, 76].

Earlier in this chapter, we have discussed evidence suggesting that executive deficits in early PD evolve differently to posterior cortically based deficits, implying a different aetiopathological basis, and this is supported by a number of neuroimaging studies. A structural MRI study has demonstrated that executive and more posterior type impairments in early PD do differ in terms of their anatomical basis, with impairment on tasks of sustained attention correlating with prefrontal atrophy, whereas verbal memory impairment correlates with hippocampal atrophy [77]. Indeed, it is well established that executive deficits are related to dysfunction within frontostriatal dopaminergic systems: functional neuroimaging studies have demonstrated reduced blood oxygen level-dependent activation in dorsolateral and ventrolateral prefrontal cortices, caudate nuclei and right putamen during performance of a working memory task in executive impaired PD patients compared with those with no cognitive impairment [78], and PET studies have demonstrated that reductions in striatal ¹⁸F-fluorodopa uptake correlate with impaired executive performance [79, 80]. However, if dopaminergic deficits do underlie the executive syndrome in PD, one might expect an improvement in executive function with levodopa. In fact, levodopa withdrawal studies report seemingly contradictory results, with dopaminergic medication improving performance on certain frontally based cognitive tasks, but leading to impairment on others [81]. This may in part be explained by the concept of an inverted U-shaped relationship between executive performance and dopaminergic activity in the prefrontal cortex, with not only low but also high prefrontal synaptic dopamine levels causing impaired performance [82] (fig. 3). Such a relationship is
consistent with experimental work involving D1 receptor-mediated modulation of dopaminergic transmission in animals [83–85] and is supported by behavioural and functional imaging studies in humans with genetically determined differences in prefrontal dopamine [86].

Evidence to support the importance of the inverted U relationship in the dysexecutive syndrome of PD comes from studies investigating a common functional polymorphism (val158met) in the catechol o-methyltransferase gene. This polymorphism alters the activity of the dopamine-regulating COMT enzyme by 40% in human cortex [87], and has a particular influence on dopamine levels in the prefrontal cortex where the expression of dopamine transporters is low relative to the striatum [88]. The low activity met/met genotype, putatively associated with higher prefrontal dopamine levels, is associated with improved performance on working memory and planning tasks in healthy controls [89], but in contrast the met/met variant is associated with impaired performance on the Tower of London planning task in early PD, and this effect is greatest in those exposed to dopaminergic medications [54]. Furthermore, functional imaging studies in early PD have demonstrated that the low activity met allele is associated not only with impaired behavioural performance on working memory and attentional set shifting tasks, but also with underactivation of a frontoparietal executive network [90, 91]. When combined with evidence from

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Fig. 2. Correlation between age and cognitive decline (change in MMSE per year) over 3.5 years depending on MAPT genotype amongst 108 incident PD patients. There is a strong correlation in H1 homozygotes, with a clear tendency to cognitive decline over the age of 70 years (Kendall’s $\tau_b = -0.35, p = 2 \times 10^{-5}$), whereas cognitive performance remains unchanged in H2 carriers, regardless of age ($\tau_b = 0.11, p = 0.36$). Reproduced from Goris et al. [74].
18F-dopa-PET studies suggesting a hyperdopaminergic state in the PFC in early PD [92–94], this work suggests that early PD patients are on the right-hand side of the inverted U-shaped curve, where higher prefrontal dopamine levels have a detrimental effect on executive performance (fig. 3). Hence, it seems that in early PD, executive deficits may relate to an upregulation of dopaminergic activity in the prefrontal cortex relative to the striatum, and are influenced by COMT genotype as well as exogenous dopaminergic medication. In later disease, dopamine levels in the PFC fall [95], and one would expect patients to shift from the right to the left hand side of the inverted U-shaped curve. Indeed, cross-sectional comparisons do indicate an alteration in the direction of the relationship between COMT genotype and executive performance in later versus early PD, and longitudinal analysis of 70 PD patients from the CamPaiGN cohort indicates that COMT met/met individuals show an improvement in executive performance over 5 years of disease progression in contrast to other genotypic groups, as predicted by the inverted U-shaped curve [20]. There may thus be a dynamic relationship between dopaminergic activity in frontostriatal networks and executive performance in PD which is dependent on disease duration, COMT genotype and medication.

Whilst less well explored, other neurotransmitter systems are also likely to be involved in cognitive dysfunction in early PD. As yet, there is little good evidence to support a role for noradrenergic and serotonergic deficits, although they have been implicated in mood and attention [17]. Cholinergic deficits do seem to be an important contributor to cognitive dysfunction in PD. Not only has cell loss in the nucleus basalis of Meynert been demonstrated in PD [96, 97], but associated cortical cholinergic deficits have been found, and a correlation between these pathological

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**Fig. 3.** Hypothesised inverted U-shaped relationship between working memory (WM) performance and dopaminergic activity in the prefrontal cortex (PFC). Evidence from behavioural and functional imaging studies in PD patients suggests that position on the curve is determined by both disease state and COMT val¹⁵⁸met genotype. Early PD patients are postulated to be on the downslope of the curve with Val homozygotes (high-activity COMT) being closer to the peak than Met homozygotes (low-activity COMT). As disease progresses, however, patients are expected to shift to the left. Reproduced with permission from Williams-Gray et al. [20].
findings and level of cognitive impairment has been reported in several studies [e.g. 98–100]. A double-blind pharmacological study has demonstrated that low-dose scopolamine, an anticholinergic, causes memory impairment in PD patients but not in healthy controls, suggesting a pre-existing subclinical cholinergic deficit in PD [101]. Functional PET studies have also confirmed a cortical cholinergic deficit in PD compared to controls, which is most pronounced in PD dementia cases [102, 103]. This has led to the use of cholinesterase inhibitors as therapeutic agents for PD dementia, although with only very modest effects [104]. Thus, although it seems very likely that cholinergic deficits are involved in the dementing process in PD and are likely to be implicated in posterior cortical deficits in early disease, there is a lack of evidence for direct correlation between cholinergic deficits and impairment in particular neuropsychological domains.

Conclusions

Early cognitive impairment probably affects around a quarter to a third of PD patients, with estimates varying according to the nature of the cohort studied and the neuropsychological criteria adopted. Agreement is yet to be reached on the most appropriate method of diagnosing ‘mild cognitive impairment’ in PD, but establishing a clear definition is important to allow selection of patients for therapeutic trials, as well as to facilitate comparison between future studies. Neuropsychological deficits in early PD include executive dysfunction, deficits in attentional shifting, poor verbal fluency, impaired explicit memory and visuospatial dysfunction. Some older cognitive screening instruments such as the MMSE are insensitive to executive deficits, and thus not well placed to assess cognition in early PD, but PD-specific screening tools have been recently developed to circumvent this problem.

Longitudinal data suggest that different types of cognitive impairment in early PD evolve in different ways. Specifically, we propose that frontostriatally based executive deficits, which are dependent on prefrontal dopaminergic activity, fluctuate and in some cases improve over time, whereas more posterior cortically based deficits herald global cognitive decline and later-occurring dementia. Genetic variation in tau, cortical Lewy body deposition, and cholinergic deficits, have been implicated in this posterior cognitive syndrome.

The direct impact of early cognitive deficits in PD on day-to-day behaviour and function is yet to be established. The focus of research to date has been on their prognostic value in terms of predicting later-occurring dementia. Interest in the concept of MCI in PD is growing, but given the heterogeneity of early cognitive deficits in PD in terms of their pathophysiology and evolution over time, subtyping of PD-MCI is essential in future longitudinal studies.
References


