

W Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease

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Cognitive impairment in patients with Parkinson's disease is gaining increased clinical significance owing to the relative success of therapeutic approaches to the motor symptoms of this disorder. Early investigations contributed to the concept of subcortical dementia associated with bradyphrenia and cognitive rigidity. For cognition in parkinsonian disorders, this notion developed into the concept of mild cognitive impairment and fronto-executive dysfunction in particular, driven mainly by dopaminergic dysmodulation and manifesting as deficits in flexibility, planning, working memory, and reinforcement learning. However, patients with Parkinson's disease could also develop a syndrome of dementia that might depend on non-dopaminergic, cholinergic cortical dysfunction. Recent findings, supplemented by advances in neuroimaging and genetic research, reveal substantial heterogeneity in the range of cognitive deficits in patients with Parkinson's disease. Remediation and management prospects for these cognitive deficits are based on neuropharmacological and cognitive rehabilitation approaches.

Introduction

Parkinson's disease is a progressive neurodegenerative disorder diagnosed on the basis of characteristic motor disturbance (bradykinesia, resting tremor, rigidity, and postural instability), asymmetrical symptom onset, and good response to levodopa.¹ As a synucleinopathy, Parkinson's disease is linked to the pathogenetic fibrillation of the unstructured soluble protein α -synuclein and the formation of Lewy bodies in nigral regions, limbic and brainstem nuclei, and neocortical regions,² although neurofibrillary tangles and plaques are also commonly present in these regions.³ Neuronal degeneration directly affects catecholaminergic (ie, dopamine and norepinephrine) and cholinergic (acetylcholine) neurotransmission. Parkinson's disease affects one out of 100 people who are aged older than 60 years in industrialised countries.⁴ Cognitive impairment, in the form of executive deficits, visuospatial and memory deficits, and clinically evident dementia, seems to be an independent non-motor aspect of the disorder that has an important role in establishing functional outcome; Parkinson's disease dementia is a crucial determinant of reduced life expectancy in patients with this movement disorder.⁵

The frequency and severity of cognitive decline caused by Parkinson's disease and its implications for clinical management emphasise the need to approach this impairment as a symptom that requires separate attention and targeted treatment. As a movement disorder, motor dysfunction is probably the most burdensome symptom for patients with Parkinson's disease. However, the relative success in managing this symptom, owing to the development of effective pharmaceutical regimens focusing on dopamine restoration, might enable a shift in attention so that the non-motor, cognitive features of Parkinson's disease can now also be effectively addressed. Increased focus on the non-motor symptoms is essential for assessing and treating the disease-specific and drug-induced psychiatric symptoms, such as depression or hallucinations, many of which are closely linked to the

cognitive symptoms and features of Parkinson's disease. Increasing evidence suggests that the neuropsychological deficits seen early in the course of the disease might also be a powerful predictor of the overall progression of cognitive dysfunction to dementia, with implications for early pharmacological intervention.

In this Review, we discuss the clinical manifestations and neurochemical features of cognitive impairment in patients with Parkinson's disease, outlining axes of cognitive disturbance. The emerging concept of heterogeneity at the levels of cognition and underlying neurochemistry, possibly a consequence of the cytologically and structurally diverse neural damage caused by the disease and its interactions with the ageing process, is supported by evidence from neuropsychological, pharmacological, neuroimaging, and genetic research. First, we concentrate on deficits in executive control—mechanisms by which performance is optimised under conditions requiring the operation of several cognitive processes. Thus, deficits in cognitive flexibility, planning, working memory, and learning appear early in Parkinson's disease and are similar to symptoms in patients with frontal lobe injury. In these manifestations of what can be broadly characterised as a fronto-striatal syndrome, deficits in the catecholaminergic, particularly dopaminergic, pathways are prominent. These aspects of cognitive dysfunction in patients with Parkinson's disease are commonly thought to be a prodrome to dementia, but their association with Parkinson's disease dementia might not be one of simple linear progression. Second, we discuss the pathological basis of the neuropsychological and debilitating clinical symptoms of dementia in patients with Parkinson's disease and the effect of non-dopaminergic, mainly cholinergic, pathological changes in extra-striatal regions.⁶ Finally, we review the clinical management of patients with Parkinson's disease and cognitive dysfunction, including dementia, with regard to its heterogeneous nature in terms of new drugs and non-pharmacological interventions.

Cognitive impairment in Parkinson's disease

Neuropsychological deficits

Controversy has surrounded the concept of cognitive deficits in Parkinson's disease since the 19th century. Contrary to James Parkinson's description⁷ in 1817 of "the senses and intellects being uninjured", Charcot,⁸ who named the disease after Parkinson, emphasised that "the mind becomes clouded and the memory is lost". More generally, the concept of mild cognitive impairment, typically used to characterise a transitional cognitive status from normal ageing to dementia, is used in Parkinson's disease as an umbrella term for the diverse neuropsychological deficits within the executive, mnemonic, and visuospatial domains.^{9–12} Patients who have been newly diagnosed with Parkinson's disease are twice as likely to develop mild cognitive impairment than are healthy elderly individuals.^{13,14} Between 20% and 57% of patients are affected by mild cognitive impairment within the first 3–5 years after diagnosis;^{15–17} therefore, this deficit deserves particular attention because of its potential predictive association with dementia.

Patients with Parkinson's disease who do not have global cognitive decline have similar patterns of impairments to those in patients with frontal lobe lesions, as assessed by use of tasks such as the Wisconsin card sorting test, the Odd-Man-Out test, and the Tower of London test,^{18–21} which index executive functions such as planning, concept formation, rule use, and working memory (the mechanism by which information is held and manipulated 'online'). These findings contributed to the emerging concept of Parkinson's disease as a fronto-striatal syndrome that gives rise to deficits that are particularly apparent when patients need to generate behaviour on the basis of internal rather than external cues^{22,23} and when they need to flexibly switch between well learned tasks.^{24,25}

In the next sections, we further discuss the manifestations of executive dysfunction revealed by neuropsychological testing (table 1) and the varied effects of dopaminergic restoration (panel 1). Although motor symptoms²⁶ and mood status, particularly depression,²⁷ have a predominantly negative effect on quality of life, executive deficits have real-world implications. Difficulties in planning during the Wisconsin card sorting test are associated with health status.²⁸ Executive impairment can be disabling as it interferes with social and occupational functioning; patients report reduced organisational skills, impaired concentration, and problems with retaining information while undertaking daily tasks.²⁹

Dopaminergic nature of the fronto-striatal dysexecutive syndrome

As well as relief from many of the motor symptoms of Parkinson's disease, dopaminergic enhancement—with the use of levodopa, dopamine receptor agonists (generally the D2 subtype), monoamine oxidase type B inhibitors, and catechol-O-methyltransferase (COMT)

inhibitors—has a parallel restorative effect on certain aspects of cognition. Evidence of dopamine-dependent cognitive deficits was initially based on reports of selective beneficial effects of drugs on tasks sensitive to frontal lobe dysfunction, either by comparing newly diagnosed (untreated) and treated patients with mild disease or by temporarily withdrawing patients from their dopaminergic regimens.^{30–33} The cognition-enhancing effects of dopaminergic drugs in patients with Parkinson's disease broadly encompass aspects of cognition that involve flexibility, for example during planning on the Tower of London test, switching between well learned tasks,²⁴ response inhibition particularly during periods of uncertainty,^{34,35} and working memory,^{32,36,37} which tap into fronto-striatal dopamine pathways.

By contrast with this dysexecutive syndrome, visuospatial function during mental rotation³⁸ and visual recognition memory, conditional associative learning, and verbal memory—amnesic features of parkinsonian mild cognitive impairment, particularly as a function of increasing clinical disability and disease

	Type of deficit	Function
Wisconsin card sorting test Tower of London test	Executive	Attention Working memory Planning Concept formation Rule use Cognitive inhibition Use of feedback
Task switching	Executive	Cognitive flexibility Response inhibition Attention Resistance to distractibility or set maintenance
Stroop performance	Executive	Attention Response inhibition
Attentional set-shifting	Executive	Attention Higher-order flexibility (stimulus dimensions) Use of feedback Resistance to distractibility/set maintenance
Reversal learning	Learning	Use of feedback Lower-order flexibility (stimulus exemplars)
Weather prediction	Learning	Use of feedback Attention Working memory Rule formation Abstract reasoning
Gambling or decision making	Impulse control	Use of feedback Response inhibition
Digit span	Memory	Working memory (numbers)
Spatial working memory	Memory	Working memory (spatial representations)
Stop signal task	Motor inhibition	Response inhibition
Delayed responding	Motor inhibition	Attention Resistance to distractibility
Mental rotation	Visuospatial	Motor imagery Visuospatial transformation

Characteristic aspects of mild cognitive impairment usually seen in patients receiving drug treatment.

Table 1: Fronto-executive deficits in early Parkinson's disease by neuropsychological task

Panel 1: Effects of dopamine restoration**Cognitive benefit or amelioration of deficit**

- Wisconsin card sorting test
- Tower of London test
- Task switching—concrete rules
- Digit span
- Spatial working memory

Cognitive deterioration from dopaminergic overdose

- Concurrent learning
- Probabilistic reversal learning
- Weather prediction classification
- Gambling and decision making
- Delayed responding with distraction
- Visual hallucinations

No effect

- Attentional set-shifting (extra-dimensional shifting)
- Task switching—abstract rules
- Pattern and spatial recognition memory
- Associative learning
- Verbal memory

Dopaminergic restoration has ameliorating, deleterious, and in some cases no effects on aspects of mild cognitive impairment that emerge during neuropsychological testing in the early stages of Parkinson's disease.

duration^{39,40}—seem to be dopamine-independent and unaffected by medication status. Dopaminergic restoration, however, might also have deleterious effects on a different subset of cognitive functions reliant on learning by integrating environmental feedback with ongoing behaviour.

The dopamine overdose hypothesis

Results from early studies indicated that dopaminergic remediation can impair some aspects of cognition, mostly by overdosing the caudate nucleus and ventral striatum, which are generally less dopaminergically depleted early in the disease.⁴¹ By contrast, the putamen is more affected by the primary dopaminergic deficit and is implicated in the motor symptoms of Parkinson's disease. Thus, by optimally titrating the dose of levodopa to ameliorate the motor symptoms, the ventral striatum and mesocortical dopaminergic pathways might be subject to an effective overdose.^{31,42} Dopaminergic dosing that restores dopamine concentrations in the severely depleted dorsal regions is thought to improve those aspects of cognition that rely on dorsal fronto-striatal circuitry; however, this dosing leads to side-effects on cognitive functions for which ventral striatal dopamine signalling, particularly the nucleus accumbens and associated fronto-striatal loops with the orbitofrontal cortex, is key. In support of this hypothesis, impulsive responding and failure to switch to a newly rewarded stimulus when the currently selected one is no longer associated with reward (reversal learning) is reported in

patients receiving treatment but not in untreated patients;^{42–45} this effect is associated with a blood-oxygen-level-dependent (BOLD) signal change on functional MRI in the nucleus accumbens but not in the dorsal striatum or frontal cortex.⁴⁶ Dopaminergic overdose has been linked to increased impulsivity and abnormal betting in a gambling setting.²⁴ In this regard, dopamine agonists such as pramipexole have been implicated in pathological gambling and dysfunction in impulse control sometimes seen in patients with Parkinson's disease,^{47,48} possibly by dopamine receptor activation outside the dorsal striatum (see also below).

The dopamine overdose rationale is central to understanding drug-induced cognitive deficits in patients with Parkinson's disease, which are typically observed during learning tasks in general, not just reversal learning. Patients with Parkinson's disease often have impairments during concurrent learning tasks for which many stimulus-outcome associations are learnt over the course of several attempts by trial-and-error feedback,⁴⁹ rather than by direct observation of the correct stimuli.^{50,51} Feedback-based behaviour implicates the mesocorticolimbic dopamine system, which includes the ventral striatum and amygdala. As such, dopaminergic drugs have been associated with adverse effects on learning in early Parkinson's disease⁵² with subtly different effects observed depending on the valence (positive/negative) of the feedback learning signal.^{53,54} Global increases in tonic dopamine that might obscure phasic stimulus-specific dopamine signals from error-correcting feedback, essential to the incremental acquisition of stimulus-outcome associations,⁵⁵ might give rise to this deficit.

Whereas drug-induced cognitive deficits are mainly associated with the context of depleted versus intact striatal regions, other deficits, such as distractibility, might stem from upregulated frontal dopaminergic transmission in early Parkinson's disease in response to reductions in striatal dopamine.⁵⁶ Untreated patients might exhibit improved frontal function, as indexed by susceptibility to distraction: one study has recently shown improved resistance to distraction on a delayed response task in the absence of dopaminergic drugs, even when compared with controls, which was not maintained after drugs were resumed, potentially suggesting that overdose at the level of the frontal cortex reinstates distractibility.⁵⁷

Dopaminergic overdosing might also account for another type of deficit in Parkinson's disease—ie, impairments in attentional mechanisms used in rule learning, as seen in weather-prediction classification tasks, in which different stimuli predict different outcomes (ie, the weather). The locus of overdose in this case might be in intact temporal regions, leading to attentional and consequent learning deficits on tasks that make use of perceptually complex stimuli.⁵⁸ Thus, impaired rule learning when this task requires the integration of non-verbal information present in such

stimuli^{59,60} might stem from an underlying attentional impairment.

Cholinergic and possible noradrenergic contributions to mild cognitive impairment in early Parkinson's disease

Results from early psychopharmacological studies have indicated that, compared with dopaminergic therapy, anticholinergic drugs lead to similar motor improvements after chronic treatment in newly diagnosed patients but impaired short-term memory³³ and frontal-like executive dysfunction after acute treatment,⁶¹ a pattern similar to that seen in patients, but not controls, after treatment with hyoscine.⁶² Cholinergic deficits at the level of the frontal and temporal cortex are well documented even early in the course of Parkinson's disease^{63–65} owing to degeneration of the basal forebrain cholinergic nuclei and ascending cholinergic pathways, which occurs in parallel with the main dopaminergic pathological changes. Neuropathological evidence lends support to a role of acetylcholine-based cognitive deficits in patients with Parkinson's disease who do not have dementia. In one study, although reduced choline acetyltransferase activity was reported in both prefrontal and temporal regions, and this was correlated with Lewy body load, only prefrontal choline acetyltransferase activity and D1 receptor density in the caudate nucleus were correlated with the extent of cognitive impairment in the absence of Alzheimer's disease pathological changes.⁶⁶ More recently, by use of acetylcholinesterase PET imaging, cholinergic denervation was reported in patients without dementia,⁶⁷ which was associated with impaired episodic verbal learning and Stroop performance⁶⁸—a task invoking executive control, or inhibition, over the prepotent reading response to a word printed in ink of an incongruent colour.

Another aspect of executive dysfunction in early Parkinson's disease is attentional set-shifting (extra-dimensional shifting), which refers to switching between higher-order modalities or classes of stimuli on the basis of feedback. Given the role of both flexibility and learning in extra-dimensional shifting, patients with Parkinson's disease unsurprisingly have reliable deficits mirroring fronto-striatal dysfunction, with cortical processing deficits associated with the degree of striatal involvement at different task stages.⁶⁹ Dopamine depletion in the caudate nucleus has no effect on extra-dimensional shifting in the marmoset;⁷⁰ similarly, switching attention between different perceptual aspects of a stimulus is insensitive to dopaminergic manipulation in Parkinson's disease,^{32,37,39,45,71} as is switching between abstract rules governing judgments of stimulus categories.²⁵ Increasing evidence⁷² suggests that norepinephrine might be implicated in this type of higher-order cognitive flexibility. This as-yet untested hypothesis is consistent with the early and profound degeneration of the locus coeruleus, the main source of cortical norepinephrine,^{73,74} seen in patients with Parkinson's disease.

Dementia in Parkinson's disease

Clinical characteristics

Although patients with Parkinson's disease dementia share some of the features of cognitive impairment seen in patients without dementia in terms of executive and mnemonic features,⁷⁵ the range, complexity, and severity of cognitive and psychiatric symptoms clearly differentiate these patients. The diagnosis of dementia in patients with Parkinson's disease is a complex undertaking despite its clear differentiation from the dementia of Alzheimer's disease, as recently highlighted by the Movement Disorder Society task force.^{76,77} The consensus criteria specify a diagnosis of Parkinson's disease according to the Queen Square Brain Bank criteria, and a dementia syndrome that is manifest in two or more cognitive domains with a decline in levels of functioning and that causes social and occupational impairment; deficits such as fluctuating attention, executive dysfunction, free recall, and visuospatial function might be seen. Patients with Parkinson's disease dementia can also have psychiatric symptoms such as depression, anxiety, excessive daytime sleepiness, and visual hallucinations (panel 2).

As Parkinson's disease dementia has been associated with mortality, longitudinal estimates of its cumulative prevalence, rather than cross-sectional estimates, are more accurate representations of true dementia frequency within the Parkinson's disease population, and range from 75% to 90%.^{78,79} Similarly, patients with Parkinson's disease are three to five times more likely to develop dementia compared with healthy individuals.^{12,80} The prevalence of Parkinson's disease dementia in the general population has been estimated at 2–3%⁸¹ and is the best predictor of admission to a nursing home.⁸²

With regards to cognitive symptoms, dementia in Parkinson's disease is closely related to dementia with Lewy bodies, although both are distinguishable from Alzheimer's disease, which involves more profound memory impairments.⁸³ Lewy bodies (a common feature in dementia disorders), plaques, and vascular changes are present in both Parkinson's disease dementia and dementia with Lewy bodies; these disorders are characterised by different temporal profiles, but whether they are separate non-converging clinical diseases remains a matter of debate.⁸⁴ In this Review, we focus on the development of dementia at least 1 year after the diagnosis of Parkinson's disease.

The association between early cognitive impairment and Parkinson's disease dementia

Parkinson's disease dementia is associated with many types of cognitive impairment, but it remains unclear whether dementia itself is indicative of further cognitive deterioration along the same impairment pathway as mild cognitive impairment in patients without dementia,^{14,85} or whether it is a separate clinical disorder⁸⁶ or an interaction between Parkinson's disease and age. Because the criteria for Parkinson's disease dementia require a diagnosis of

Panel 2: Diagnostic criteria, neuropsychological features, and psychiatric symptoms of Parkinson's disease dementia

Diagnostic criteria

- Diagnosis of Parkinson's disease according to Queen Square brain bank criteria
- Parkinson's disease precedes dementia onset
- MMSE score of <26
- Severe cognitive dysfunction that interferes with daily living
- Impairment on at least two of the following: three-word recall (MMSE), overlapping pentagons (MMSE), months reversed or sevens backward (MMSE), lexical fluency, or clock drawing
- Absence of major depression, delirium, or other abnormalities that obscure diagnosis

Neuropsychological deficits

- Executive: Wisconsin card sorting test, Stroop performance, Odd-Man-Out, verbal fluency (semantic, phonological)
- Working memory: digit and spatial span
- Memory: free and cued recall, auditory verbal learning
- Visuospatial abilities: clock drawing, Benton line orientation, face recognition, fragmented letters

Psychiatric symptoms

- Visual hallucinations
- Psychosis
- Apathy
- Depression
- Anxiety

MMSE=mini-mental state examination.

Parkinson's disease before dementia onset, patients with early signs of dementia before or in the absence of a diagnosis of Parkinson's disease would not be considered for inclusion in an epidemiological or longitudinal study that attempted to address this issue. For example, subtle memory deficits are seen in early Parkinson's disease and equivocal findings have been reported with regard to verbal and visual memory deficits in early Parkinson's disease dementia,⁸⁷⁻⁹¹ consistent with temporal lobe denervation (see below). The distinct pathological features of Alzheimer's disease⁹² might contribute to some aspect of memory dysfunction in Parkinson's disease dementia,⁹³ but this cognitive impairment is overall milder than in Alzheimer's disease.⁹⁴ Whether mnemonic deficits in Parkinson's disease dementia are independent of the executive impairment and fluctuating attention,⁹⁴ which precede and eventually precipitate the dementia diagnosis, is unclear.

Moreover, age has a substantial effect on Parkinson's disease dementia.⁹⁵ Despite the large variability in the timing of dementia onset, from a few years to two decades from the diagnosis of Parkinson's disease, age at onset

and consequent duration of Parkinson's disease seem to make no notable contribution beyond age itself;⁹⁶ young patients with early-onset Parkinson's disease, and therefore with longer disease duration, have low rates of dementia. In a recent study⁹⁷ on the neuropathological changes observed in the final phase of Parkinson's disease at different ages, two clinical milestones of advanced disease, dementia and visual hallucinations, were associated with cortical Lewy body load and greater Alzheimer's disease-type pathological changes, but overall no differences were seen as a function of age. Only in the early-middle phase, before dementia and visual hallucinations develop, did age affect rate of disease progression; pathological changes progressed uniformly in the advanced stage irrespective of the age at onset. Parkinson's disease has been proposed to progress exponentially, so that ageing leads to a longer disease course in young-onset patients, accelerating clinically when the advanced stage is reached to match that of older-onset cases.⁹⁷ This exponential clinical effect might not be attributable to the actual rate of neurodegeneration in Parkinson's disease as such, but could result from an exponential increase in the number of neurons affected during the regional transition of the disease from the brainstem nuclei to the neocortex.

Data from many studies lend support to a predictive association between the executive dysfunction of mild cognitive impairment in early Parkinson's disease and Parkinson's disease dementia, highlighting deficits in verbal fluency, abstract reasoning,⁹ picture completion,¹⁰ and Stroop performance^{10,98} as prognostic of dementia onset. However, the nature of neuropsychological deficits that are prodromal to dementia might differ as a function of their temporal distance from development of dementia; moreover, the meaningfulness and practical use of an association between Parkinson's disease dementia and perseveration on the Wisconsin card sorting test observed within just 1 year of dementia onset⁹⁹ might be limited.

Data from other studies, however, have indicated that the profile of impairment in patients who eventually develop dementia might differ from the typical frontostriatal executive dysfunction seen in early Parkinson's disease,¹⁵ emphasising the role of visuospatial and language deficits in these patients that are indicative of early Lewy body load in the occipito-parietal cortex and the temporal lobe. This differing profile is highlighted in the Parkinson's disease dementia criteria of the Movement Disorder Society, and data from our studies have indicated that impairment on two simple bedside assessments—pentagon copying from the mini-mental state examination¹⁰⁰ and semantic fluency—predict cognitive decline and Parkinson's disease dementia at 3-year and 5-year follow-up.^{15,101} Defining the pattern of mild cognitive impairment that is prodromal of Parkinson's disease dementia is an area of active research owing to its predictive value and the possibility that these deficits could respond better to treatments used in dementia such as cholinesterase inhibitors and memantine (see below).

Neuroimaging findings in Parkinson's disease dementia

Neuroimaging evidence complements these neuropsychological findings, suggesting that both widespread pathological changes and specific regional changes in the brain underlie early mild cognitive impairment before Parkinson's disease dementia develops. Reduced cerebral glucose uptake in extensive posterior cortical areas, particularly in the occipitoparietal junction and temporal cortex, occurs in patients with Parkinson's disease and mild cognitive impairment compared with cognitively intact patients.^{102,103} Widespread changes in fractional anisotropy measures from diffusion tensor MRI are more prominent in mild cases of non-tremor-dominant Parkinson's disease than in tremor-dominant and mixed profile Parkinson's disease, potentially reflecting diffuse grey matter loss¹⁰⁴ that might also predict subsequent cognitive decline.

In established Parkinson's disease dementia, substantial atrophy is seen throughout the brain, particularly in the frontal, temporal, and occipital cortices and in subcortical regions.¹⁰⁵⁻¹⁰⁹ In one study, reductions in grey matter in the occipital cortex bilaterally differentiated Parkinson's disease dementia from Parkinson's disease.¹¹⁰ In another study, which accounted for atrophy changes, decreased blood flow in posterior parieto-occipital regions, particularly the precuneus, was reported in patients with Parkinson's disease dementia but not in patients with Alzheimer's disease for whom posterior cingulate changes were reported instead.¹¹¹ Although increased concentrations of cortical amyloid have been reported in patients with dementia with Lewy bodies,¹¹² but not in patients with Parkinson's disease dementia,¹¹³ it is unclear whether amyloid deposition is a time-dependent process, and therefore different in dementia with Lewy bodies and Parkinson's disease dementia, which have different dementia time courses. Amyloid might have a greater role with shorter time to dementia onset, a hypothesis that is supported by clinicopathological findings of increased amyloid and α -synuclein concentrations in patients with dementia with Lewy bodies and Parkinson's disease dementia of shorter disease duration compared with patients with Parkinson's disease dementia who have a longer motor symptom history before dementia onset.¹¹⁴ Establishing the cortical amyloid burden in Parkinson's disease dementia and whether it affects the clinical phenotype is important when evaluating the benefits of anti-amyloid strategies in Parkinson's disease dementia.

Visual hallucinations also predict rapid cognitive deterioration and dementia onset in Parkinson's disease.^{115,116} Visual hallucinations are associated with cortical Lewy bodies¹¹⁷ particularly in temporal regions.¹¹⁸ Hippocampal atrophy is associated with verbal learning deficits in patients with Parkinson's disease dementia who have hallucinations.¹¹⁹ Compared with patients who do not have hallucinations, patients with visual hallucinations also have frontal hypermetabolism¹²⁰ and orbitofrontal

atrophy that correlates with visual memory deficits.¹²¹ Nonetheless, visuospatial and perceptual deficits are more frequently observed in patients with Parkinson's disease dementia with visual hallucinations,^{122,123} similar to the prominent pathological changes in the visual association area, discussed previously. Visual hallucinations in Parkinson's disease dementia might therefore have a complex neural origin, and visual, temporal, and frontal areas might also be implicated, depending on the criteria used to specify the Parkinson's disease dementia and control groups.

Cholinergic dysfunction in Parkinson's disease dementia

Cholinergic deficits stem from degeneration and Lewy body pathological changes in the basal forebrain and ascending cholinergic pathways, which can be even more pronounced in patients with Parkinson's disease dementia than in patients with Parkinson's disease or Alzheimer's disease,¹²⁴⁻¹²⁹ affecting the frontal, parietal, and temporal cortices and the amygdala. These in-vivo neuroimaging studies were preceded by early post-mortem findings from patients with Parkinson's disease dementia of reduced choline acetyltransferase concentrations, particularly in the temporal cortex, which were associated with the extent of cognitive impairment and the size of the surviving neuronal population of the basal forebrain nucleus of Meynert.¹³⁰ The onset of dementia was also associated with profound basal forebrain cholinergic degeneration.⁶⁵ By contrast, nigrostriatal dopaminergic degeneration is indistinguishable between Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies.¹³¹ Cholinergic abnormalities are also thought to underlie visual hallucinations in Parkinson's disease dementia.¹³²⁻¹³⁴ In the past 10 years, cholinesterase inhibitors, discussed below, have been recognised to confer moderate benefits to patients with Parkinson's disease dementia,¹³⁵ at least early in the course of dementia.

Genetic susceptibility factors

Research on genetic susceptibility to Parkinson's disease dementia has been inconclusive, although a family history of Parkinson's disease^{136,137} might increase the risk for developing dementia. Some studies have focused on α -synuclein and tau, which might be involved in this process, suggesting that common variation in both the *SNCA* (α -synuclein) and the *MAPT* (microtubule-associated protein tau) H1 haplotype might not only affect susceptibility to sporadic Parkinson's disease, but also affect the rate of cognitive decline and Parkinson's disease dementia.^{101,138-140} Moreover, tau has been linked to cholinergic neurotransmission via the K allele of the butyrylcholinesterase gene (*BCHE*), which is relevant to cognitive impairment in Alzheimer's disease¹⁴¹ and reduces tau phosphorylation rate, and hence directly affects Lewy body formation.¹⁴² The apolipoprotein E ϵ 4 (*APOE* ϵ 4) allele, which increases vulnerability to Alzheimer's disease and predicts cholinergic deficits,¹⁴³

has also been equivocally associated with Parkinson's disease dementia,^{80,144} although large-scale studies are needed to clarify this.¹⁴⁵ Cognition in patients with Parkinson's disease dementia carrying both the *APOE* $\epsilon 4$ allele and the *BCHE* K allele might deteriorate more rapidly than in other patients,¹⁴⁶ although the underlying mechanism is unclear. Finally, glucocerebrosidase mutations implicated in Lewy body formation might increase the risk for both Parkinson's disease dementia and dementia with Lewy bodies;^{147,148} in one study, hallucinations and dementia were reported in about 45% of mutation carriers. More work is needed to understand the genetic contributions to Parkinson's disease dementia with large-scale, adequately powered longitudinal studies that focus on common or more frequent mutations in relevant genes to account for variation in cognitive decline in the wider Parkinson's disease population.

Heterogeneity in cognitive profiles

The association between mild cognitive impairment in patients with and without dementia is far from straightforward. Although cognitive impairment, particularly in the form of early-stage executive dysfunction, is fairly common in Parkinson's disease and well documented neurally and neurochemically, it is not universal or uniform; patients have diverse impairment profiles with variable risk and progression rate to dementia. The basis of this heterogeneity is unclear but might be at least partly explained by uneven dopamine loss across the basal ganglia circuitry^{149,150} and neurodegenerative hallmarks such as the emergence of cortical Lewy bodies and non-Parkinson's disease features as a consequence of ageing,⁹⁷ which might interact with the putative pathological processes that underlie dementia.

Recent genetic findings in patients with mild Parkinson's disease without dementia point to the role of catecholaminergic metabolism and its modulation by the COMT Val158Met polymorphism in executive dysfunction. Results from behavioural and genetic imaging studies have indicated that the COMT genotype might affect performance on tasks sensitive to fronto-striatal dysfunction such as the Tower of London test.^{151–153} Early Parkinson's disease is characterised by a basal hyperdopaminergic state in the prefrontal cortex, which might change as the disease progresses and be subject to modulation by COMT and dopaminergic drugs. Dopamine-dependent executive dysfunction in Parkinson's disease has been proposed to occur as a function of these factors,^{151,154} and relates to the notion of optimum dopamine concentrations in the prefrontal cortex; cognitive functions such as executive control reliant on this circuitry are adversely affected by too high or too low dopamine neurotransmission. The COMT genotype affects frontoparietal activity during planning in the Tower of London test, presumably reflecting changes in cortical dopamine modulation. Although these findings link the COMT polymorphism with dopamine-specific effects, all

catecholaminergic neurotransmission, including noradrenergic, is also affected by this polymorphism.¹⁵⁵ Further replication in other cohorts of patients will strengthen the case for an association between the COMT mutation and the dysexecutive syndrome in Parkinson's disease.

In addition to understanding cognitive heterogeneity observed at any one point between patients, data from large cohort studies with longitudinal follow-up have indicated different patterns of disease progression over time. For example, in a subgroup of patients with dopamine-unresponsive axial features such as postural instability and gait disturbance, there is a greater tendency to develop dementia earlier in the disease course,^{14,15,156,157} and results from other studies have shown that dementia is rare in patients with tremor-dominant Parkinson's disease.¹⁵⁸ The basis for this finding is unclear but seems likely to relate to early notable non-nigral pathological changes, particularly Lewy body formation in extra-nigral sites, including the pedunculopontine nucleus¹⁴⁹ and neocortex. The Sydney multicentre study¹⁵⁹ is unique in its clinicopathological insights based on the 20-year longitudinal follow-up of a large cohort. In this study, three distinct groups were identified: one group with severe neocortical Lewy body disease consistent with the profile of dementia with Lewy bodies, a younger-onset group with longer survival and typically slow clinical course progressing caudorostrally from the brainstem, and a third group with late-onset disease who had a faster rate of progression to dementia, with limbic and neocortical pathological changes. Taken together, these findings indicate the existence of meaningful subdivisions in the presentation and progression of cognitive dysfunction in patients with Parkinson's disease.

The heterogeneity characteristic of cognitive impairment in Parkinson's disease, with its varied neuropsychological and clinical manifestations and diverse underlying neurochemistry, is summarised in the figure. Neuropsychological overlap exists because patients with Parkinson's disease and dementia, with their pronounced acetylcholine-based visuospatial and memory deficits, also have dopamine-dependent executive deficits, secondary to nigrostriatal degeneration that underlies their diagnosis of this disorder. Because Parkinson's disease affects many of the neurotransmitter systems of the reticular core in addition to nigrostriatal dopamine, noradrenergic imbalance might contribute to a different subset of executive deficits, and some degree of frontal cholinergic deficit might also contribute to cognitive impairment early in the disease course.

To establish the development of cognitive impairment in Parkinson's disease empirically, pharmacological—ie, catecholaminergic and cholinergic—manipulations could be systematically applied longitudinally in a large patient cohort versus a matched control population to assess possible interactions with ageing. The possible contributions of interactions at the neurotransmitter level also need to be taken into account. As some

symptoms of Parkinson's disease dementia seem to be sensitive to cholinergic manipulations, at least in some patients and particularly early in the disease course, more than just the obvious interpretation of a central profound cholinergic deficit is implied; boosting cholinergic neurotransmission might mitigate the effects of encroaching cortical and subcortical denervation, by enhancing the function of a degenerating cortex or by interacting with other failing neurotransmitter systems. We concede that this complex picture might only be deciphered by taking into account variation not only at the phenotypic level, but also at the genotypic level.

Clinical management

Dopaminergic treatments of cognitive deficits

Therapeutic intervention in Parkinson's disease dementia is structured around treatment of the motor impairment and non-motor symptoms of sleep disturbance, gastrointestinal problems, and depression. Because these features ultimately have the greatest effect on patients' quality of life, symptom relief and promotion of functional independence is of great importance. An overall strategy of delaying the use of levodopa¹⁶⁰ avoids or postpones the development of motor complications, drug intolerance, and cognitively detrimental side-effects. From this point of view, amelioration of the executive fronto-striatal deficits seems to be a noteworthy, although possibly secondary, consequence of the central dopaminergic treatment strategy. Factors such as age and disease severity,¹⁶¹ as well as the COMT polymorphism, interact with dopaminergic regimens and contribute to subtle differences in the cognitive profile of patients with Parkinson's disease without dementia. Recent concerns about the use of dopaminergic agonists in the development of pathological gambling, impulse control, and repetitive behaviours extend the implications of the dopamine overdose hypothesis from the cognitive to the psychiatric domain.^{162,163} Factors such as male sex, novelty-seeking behaviour, impulsivity, and family history of addictive behaviour seem to be associated with these side-effects.¹⁶⁴

Although dopaminergic drugs are known to ameliorate some cognitive deficits in Parkinson's disease, as has already been discussed, consideration of these benefits has limited relevance to prescribing practice for patients with advanced disease and neuropsychiatric symptoms. Despite the fact that hallucinations in Parkinson's disease implicate dopaminergic, cholinergic, and serotonergic imbalances, agonist-induced dopaminergic overdose is associated with hallucinations in Parkinson's disease.¹⁶⁵⁻¹⁶⁸ Pramipexole, a D2/D3 agonist, has harmful effects on cognition,^{48,169} causing additional deficits in verbal fluency, executive function, and verbal short-term memory compared with pergolide, which acts on D1/D2 receptors.^{170,171}

In addition to its main dopaminergic features, executive impairment in early Parkinson's disease might have a noradrenergic component, expressed as higher-order

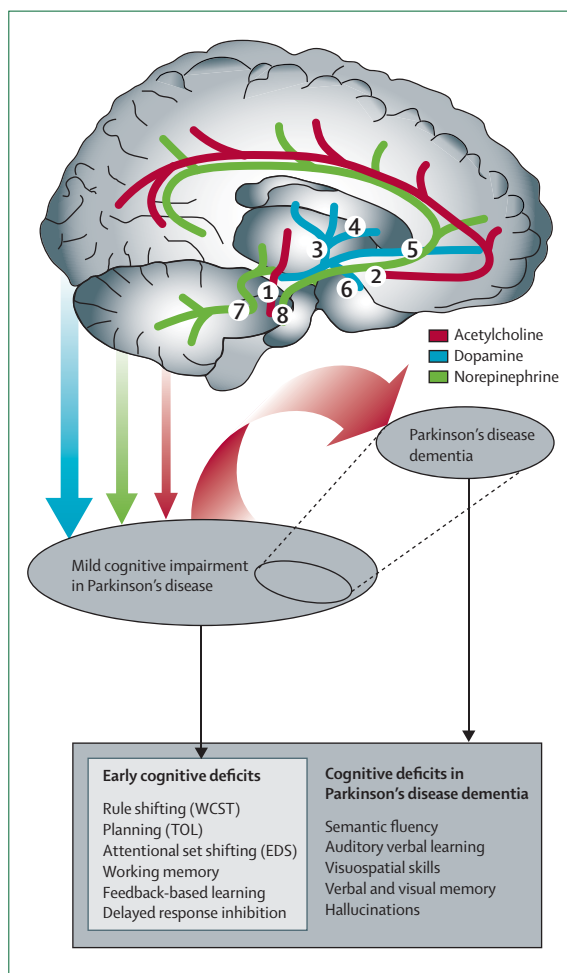


Figure: Cognitive impairment in Parkinson's disease

The neuropsychological deficits characterising the dysexecutive syndrome in the mild cognitive impairment of early Parkinson's disease are mediated mainly by fronto-striatal dopaminergic dysfunction (blue). Noradrenergic dysfunction (green) probably underlies the attentional set shifting deficit, which forms part of the dysexecutive syndrome, although this remains untested in Parkinson's disease. Some frontal cholinergic deficit (red) also compromises early Parkinson's disease cognition. Although diffuse cortical degeneration is seen in Parkinson's disease dementia, its distinctive visuospatial and mnemonic deficits indicate cholinergic involvement. Cholinergic modulation probably has a key role in the progression to Parkinson's disease dementia (red arrow). Neuropsychological deficits are shared with those of the frontal dysexecutive syndrome (overlapping boxes of cognitive deficits), which indicate the primary catecholaminergic and comparatively circumscribed cholinergic pathological changes of early Parkinson's disease. Pathways outlined on the brain section are those compromised by the disease and likely to be implicated in cognitive impairment. The cholinergic pathways are from the pedunculopontine nucleus to the thalamus (1) and from the basal nucleus of Meynert to the neocortex (2). The dopaminergic pathways are the nigrostriatal, from the substantia nigra (pars compacta) to the striatum (3); mesolimbic, from the ventral tegmental area to the nucleus accumbens (4); mesocortical, from the ventral tegmental area to the frontal cortex (5); and tuberoinfundibular, from the hypothalamus to the pituitary gland (6). The noradrenergic pathways are from the lateral tegmental nucleus to the amygdala and hippocampus (7); and from the locus coeruleus to the hypothalamus, thalamus, amygdala, cortex, and cerebellum (8). Serotonergic deficits are also present in Parkinson's disease (not shown). WCST=Wisconsin card sorting test. TOL=Tower of London test. EDS=extra-dimensional shifting.

cognitive flexibility deficits. In an 8-week, dose-flexible pilot study, atomoxetine, a norepinephrine-reuptake inhibitor licensed for the treatment of attention-deficit hyperactivity disorder, improved executive function, attention, and verbal memory in patients with Parkinson's disease,¹⁷² suggesting a novel treatment approach for the cognitive sequelae of noradrenergic dysfunction in this disease.

Cholinergic treatment of cognitive deficits

By contrast with the early executive deficits, deliberate attention has been given to the pharmacological management of Parkinson's disease dementia owing to its devastating and pervasive effect on patients and caregivers. Cholinesterase inhibitors, a class of drugs typically used in the management of Alzheimer's disease, can be used with modest benefit in Parkinson's disease dementia, at least in the early stages, with few side-effects (table 2).^{177–179} Rivastigmine, a dual inhibitor of acetylcholinesterase and butyrylcholinesterase, improves dementia symptoms mainly by ameliorating the fluctuating attention that interferes with the simplest of tasks in patients with Parkinson's disease dementia, while only slightly increasing tremor.^{135,180} In one study, rivastigmine improved activities of daily living in Parkinson's disease dementia relative to baseline, but only stabilised patients with Alzheimer's disease, and the presence of visual hallucinations predicted treatment response.¹⁸¹ Other cholinesterase inhibitors, such as donepezil, also improve cognition, as measured by mini-mental state examination scores and clinicians' interview-based impression of change with caregiver input, without exacerbating parkinsonism.¹⁷³ Galantamine, with its additional nicotinic action, ameliorates dementia but might be associated with adverse physical side-effects.¹⁷⁴

Consequently, anticholinergic drugs, which have typically been used to target tremor in Parkinson's disease, have the most adverse effects with regard to dementia¹⁶⁰ and are a substantial risk factor for Parkinson's disease dementia. Prolonged use of these drugs is associated with increased frequency of cortical plaques and tangles in patients with Parkinson's disease without dementia,¹⁸² thus any disease-modifying benefit is outweighed by the risk of these side-effects.

In addition to cholinesterase inhibitors, NMDA receptor antagonists are also proving clinically relevant for the management of Parkinson's disease dementia. Amantadine might delay and attenuate the severity of dementia in Parkinson's disease,¹⁷⁶ but can induce hallucinations and confusion in patients with advanced disease. Memantine, a glutamatergic compound and non-competitive antagonist of nicotinic acetylcholine receptors, has ameliorated cognitive impairment in Parkinson's disease dementia in recent trials.^{175,183}

Cognitive rehabilitation

Pharmacotherapy can be complemented by the provision of psychosocial support and cognitive rehabilitation through structured training programmes. In patients with Parkinson's disease without dementia, cognitive training that targeted attention, abstract reasoning, and visuospatial abilities improved aspects of cognition reliant on frontal function.¹⁸⁴ Results from this preliminary study indicated lasting improvements compared with baseline verbal fluency and recall, emphasising the importance of continued mental stimulation in the preservation of cognitive capacity. We are not aware of other similar studies in Parkinson's disease dementia and, in this regard, evidence from a study in patients with Alzheimer's disease and mild cognitive deficits who received cholinesterase inhibitors might be relevant.¹⁸⁵ In this study, training on

	Neurochemical action	Study design*	n (total)	Moderate clinical benefits
Rivastigmine	Dual acetylcholinesterase and butyrylcholinesterase inhibition	Randomised, placebo-controlled trial ¹³⁵	410	ADAS-Cog, ADCS-activities of daily living, MMSE, verbal fluency, attention, clock drawing
Donepezil	Acetylcholinesterase inhibition	Double-blind, randomised, placebo-controlled, crossover trial ¹⁷³	14	MMSE, CIBIC+
Galantamine	Acetylcholinesterase inhibition, nicotinic acetylcholine receptor stimulation	Open-label placebo-controlled trial ¹⁷⁴	41	MMSE, NPI, clock drawing, reduction in sleep disturbance, anxiety, hallucinations
Memantine	NMDA receptor antagonist, nicotinic acetylcholine receptor antagonist	Double-blind, randomised, placebo-controlled, multicentre trial ¹⁷⁵	72 patients with Parkinson's disease dementia or dementia with Lewy bodies	CGIC, attentional speed
Amantadine	NMDA receptor antagonist	Retrospective study involving survival analysis of a group of patients with Parkinson's disease ¹⁷⁶	593	Greater MMSE and slower cognitive decline to dementia endpoint

*Only representative studies are shown. ADAS-Cog=Alzheimer's disease assessment scale-cognitive subscale. ADCS=Alzheimer's Disease Cooperative Study. MMSE=mini-mental state examination. CIBIC+=clinicians' interview-based impression of change with caregiver input. NPI=neuropsychiatric inventory. CGIC=clinical global impression of change.

Table 2: Targeting cholinergic and glutamatergic imbalance in the early stages of Parkinson's disease dementia can confer modest benefits to overall functioning

recall, orientation, and functional tasks (eg, paying bills) resulted in greater improvement compared with a simple programme of therapist-led mental stimulation, and this improvement was maintained even at a 3-month follow-up. These approaches are becoming increasingly relevant to progressive neurodegenerative disorders with cognitive and psychiatric symptoms such as Parkinson's disease dementia and could be tailored to the needs of cognitively impaired patients with Parkinson's disease, particularly early in the course of dementia. For example, such a programme could incorporate strategies that promote physical independence by focusing on walking difficulties faced by patients with visuospatial deficits. A large cluster randomised controlled trial⁸⁶ across urban residential sites for patients with dementia studied the effects of person-centred care and dementia care. Although non-specific intervention effects were not controlled for, there were reductions in agitation and prescription of psychotropic drugs, highlighting new ways of improving the quality of life of patients with dementia.

Conclusions

In this Review, we have outlined cognitive decline in Parkinson's disease in terms of various neuropsychological and neurochemical pathways (figure). Early cognitive impairment, particularly in the form of executive dysfunction, is indicative of mainly fronto-striatal pathological changes and might originate in nigrostriatal and subsequent mesocortical dopamine denervation rather than cortical Lewy body formation. A potential parallel noradrenergic deficit, stemming from coeruleal degeneration, and the inevitable effect of circumscribed cholinergic disturbance in patients without dementia might also contribute to mild cognitive impairment in early Parkinson's disease. Cognitive impairment in some patients might be constrained to manageable executive and memory deficits. Others, in whom extensive Lewy body pathological changes lead to widespread cortical and subcortical degeneration and a profound cholinergic deficit, might develop dementia. Some aspects of mild cognitive impairment in early Parkinson's disease can be prodromal to dementia, but its association with this qualitatively distinct, severe level of dysfunction is unclear, as is the role of cholinergic deficits in its expression. Pharmacological amelioration of the executive deficits is mostly a typical consequence of the dopaminergic regimen that targets motor symptoms, whereas cholinesterase inhibitors are the treatment of choice for early-stage Parkinson's disease dementia. Advances are being made in disentangling the cognitive phenotypes of Parkinson's disease, but large longitudinal studies are needed to understand the specific neurochemical and neuropathological bases of cognitive impairment. Early identification of patients at risk of severe cognitive impairment and dementia will help to better inform choice of pharmacotherapy and aid a personalised approach to treatment.

Search strategy and selection criteria

References for this Review were identified through searches of PubMed from 1966 to August, 2010, with the search terms "Parkinson's disease", "mild cognitive impairment", "Parkinson's disease dementia", "bradyphrenia", "age", "executive", "memory", "visuospatial", "epidemiology", "longitudinal", "dopamine", "acetylcholine", "noradrenaline", "genes", and "neuroimaging" as combined main keywords. Articles were also identified through searches of the authors' own files. Only papers published in English were reviewed.

Contributors

AAK prepared the paper with guidance and comments from TWR and RAB.

Conflicts of interest

TWR is co-inventor of the CANTAB neuropsychological test battery and consultant share option holder for Cambridge Cognition. He also consults for Allon Therapeutics, Eli Lilly, Lundbeck, and Roche, and is a member of the Pfizer Scientific Advisory Board. TWR has received research grants from GlaxoSmithKline and Eli Lilly while working at the Department of Experimental Psychology, University of Cambridge, UK. AAK and RAB have no conflicts of interest.

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