REVIEW

# Cognitive Deficits in Parkinson's Disease: A Cognitive Neuroscience Perspective

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**ABSTRACT:** Progress in characterization of the nature, neural basis, and treatment of cognitive deficits in Parkinson's disease is reviewed from the perspective of cognitive neuroscience. An initial emphasis on *fronto-striatal* executive deficits is surveyed along with the discoveries of disruption as well as remediation of certain impairments by dopaminergic mediation and their association with theories of reinforcement learning. Subsequent focus on large cohorts has revealed considerable heterogeneity in the cognitive impairments as well as a suggestion of at least two distinct syndromes, with the dopamine-dependent fronto-striatal deficits being somewhat independent of other signs commonly associated with Parkinson's disease dementia. The utility is proposed of a new, integrated cognitive neuroscience approach based on combining genetic and neuroimaging methodologies with neuropsychological and, ultimately, psychopharmacological approaches.


**Key Words:** cognition; memory; attention; executive function; dopamine; prefrontal cortex; striatum

The subject of cognitive deficits in Parkinson's disease (PD) has been a matter of some controversy since the initial description of the disease.[1,2] There was a period in the 1980s in which the presence of cognitive impairment in PD as well as the very functions of the basal ganglia in cognitive functioning were questioned. Neither of these issues is seriously doubted today. Cognitive deficits as well as frank dementia are well documented in PD and are now considered to be among the most important symptoms of perhaps the greatest clinical unmet need. However, debate about the precise nature of these cognitive impairments, their consistency in the disease, and their neural mediation has ranged widely. Here, we summarize these various stages of debate from the perspective of cognitive neuroscience and then focus on the contemporary state of play. A combination of neuropsychological, genetic, neuroimaging, and psychopharmacological elements of an integrated cognitive neuroscience approach has resulted in a re-evaluation of the utility of PD as a *model basal ganglia disorder* that has enabled study of the functions of the human striatum as well as its ascending dopaminergic innervation. Instead, a new program for assessing and predicting the heterogeneity of cognitive deficits in PD has arisen aimed at characterizing their underlying neural substrates and genetic influences and, ultimately, their remediation.

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## Cognitive Deficits in PD: Evolution of Ideas and Hypotheses

The initial controversy concerning cognition in PD was about the nature of the deficits and whether they differed from those of dementia. An obvious distinction was between *declarative* versus *procedural* (or

*nondeclarative*) modes of processing.[3] Medial temporal lobe damage (including to the hippocampus) was associated with the former, and basal ganglia impairments were associated with the latter. Hence, PD would not be expected to produce major impairments in *declarative* modes of processing such as episodic memory but, rather, in *nondeclarative* memory, including examples of procedural memory such as perceptual and skill learning. Furthermore, the discovery of close anatomical associations of cortico-striatal circuitry, with the prefrontal cortex (PFC) being a major target of so-called parallel segregated pathways,[4] suggested that the nature of parkinsonian deficits would be *fronto-executive* in nature. These speculations were largely borne out by a series of detailed studies on patients with PD at various stages, including never-medicated patients, patients early in the disease course, and medicated patients with various disease durations varying from 1 to 15 years, which demonstrated impairments in such functions as planning, working memory, attentional set-shifting (as in the Wisconsin Card Sort Test), memory recall, verbal fluency, and Stroop-like processing (involving attentional conflict) as well as in many aspects of motor cognition.[5-25] To these impairments, perhaps surprisingly, deficits of *inhibitory* functioning were added somewhat later, notably the stop-signal reaction time task.[26] Our own approach, based in part on the Cambridge Neuropsychological Test Automated Battery (CANTAB) (available at: http://www.camcog.com/cantabtests.asp),[13,17,21] utilizes computer tests implemented with a touch-sensitive screen designed to capitalize on what is known about the neuropsychological bases of cognition in experimental animals. However, this approach to assessment can readily be combined with the more traditional measures and with the novel test procedures devised, for example, for functional neuroimaging methods. In most of the early studies, memory impairments were limited to working memory and free recall-type scenarios rather than involving, for example, recognition memory, except in the case of patients with more severe PD who had evidence of dementia. Also notable was the existence of cognitive impairments that somehow appeared to parallel the motor ones, for example, in terms of slowed thinking (*bradyphrenia*[21,27]) (compared with bradykinesia), cognitive inflexibility[17] (to be compared with akinesia or motor rigidity) and perseveration (similar but not identical to the set-shifting problems seen in patients with frontal lobe lesions.[28] Some of these deficits appeared to be remediated later in the course of the disease, when levodopa (L-dopa) medication regimes had been established.[17,20]

Thus, those studies raised new questions concerning the role of dopamine in such cognitive impairments. The classic study by Brozoski et al.[29] concerning the deleterious effects of prefrontal dopamine depletion in rhesus monkeys on the "working memory" requirements of the spatial delayed response task had clearly indicated a potential role for this chemical neurotransmitter in aspects of cognition, because the working memory impairments responded in some cases to treatment with dopaminergic agonists.

However, there had been relatively few studies of the same PD patients being tested both *on* and *off* L-dopa. One of those[14] had demonstrated no clear benefits of medication either on fluency or on a complex learning task; in fact, there were clear suggestions of some *deficits* arising from L-dopa medication. Another study by Lange et al.[20] in patients with relatively severe PD demonstrated that both spatial working memory and planning (on the Tower of London test) exhibited improvements on L-dopa. In the case of planning, both the accuracy and the speed of thinking when solving the problems appeared to be enhanced. On the other hand, there was no clear improvement in attentional set-shifting (although early learning of the constituent visual discriminations with feedback was improved), and visual recognition memory (which was certainly deficient compared with controls) exhibited no significant benefit whatsoever. Whereas later findings from medication withdrawal studies have tended to confirm a beneficial effect of L-dopa on spatial and verbal working memory,[30] probably acting within the fronto-striatal circuitry,[31,32] no such improvement has been observed for the extra-dimensional shifting impairment.[30,33]

These findings, therefore, raised the possibility that some of the impairments were dopamine-independent in nature and perhaps were attributable instead to the many other aspects of neurochemical pathology by then shown to be occurring in PD, including to the ascending noradrenergic, serotoninergic, and cholinergic neurotransmitter systems to the forebrain[34-39] as well as to the potentially deleterious effects of Lewy body pathology, for example, in the cerebral cortex[40] (Fig. 1).

## Cognitive Deficits in PD Arising From Dopamine Medication

Although some of the beneficial effects of L-dopa on aspects of cognition were later confirmed,[41] it was clear that this was far from being a simple story. Taking up the impetus provided by their early study,[14] Swainson et al.[41] observed surprising deficits in a test of cognitive flexibility involving reversal learning in the same medicated PD patients who appeared to show benefit on tests of short-term spatial memory. Thus, what was good for certain forms of memory was bad for certain aspects of learning involved in overcoming prepotent learned tendencies. Those authors invoked the Yerkes-Dodson inverted U-shaped functions to explain the pattern of impairments; thus, reversal learning hypothetically depended on more ventral regions of the striatum that were known to be

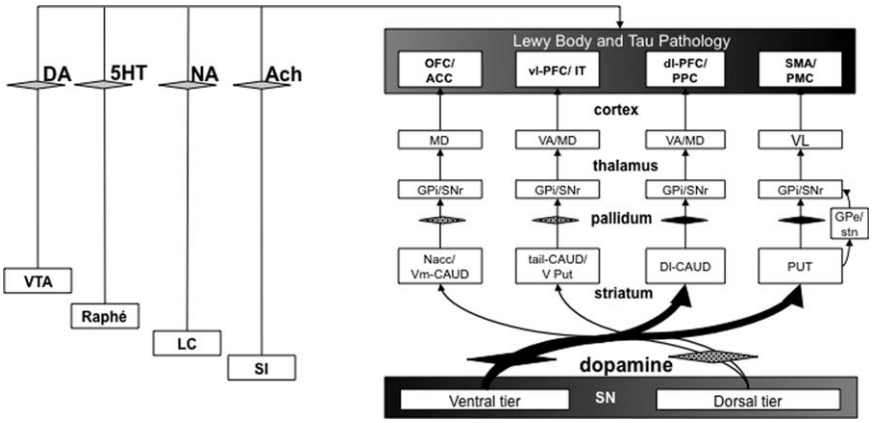


**FIG. 1.** This is a schematic of the chemical neuropathology of Parkinson' disease (PD), as distributed across several corticostrial "loops." The degree of shading indicates the severity of cell damage (in the substantia nigra [SN]) and dopamine deficiency (in other areas). Also highlighted are the presence of Lewy body and tau pathology in the cortex (extending to the posterior cortex; not shown here) and effects on the mesocortical dopamine (DA) projection from the ventral tegmental area (VTA), the serotonergic (5HT) projection from the raphé nuclei, the noradrenergic (NA) projection from the locus coeruleus (LC), and the cholinergic (Ach) input from the basal forebrain or substantia innominata (SI). OFC indicates orbitofrontal cortex; ACC, anterior cingulate cortex; vl-PFC, ventrolateral prefrontal cortex; IT, inferotemporal cortex; dl-PFC, dorsolateral prefrontal cortex; PPC, posterior parietal cortex; SMA, supplementary motor area; PMC, premotor cortex; MD, dorsomedial nucleus of thalamus; VA, ventral anterior thalamus; VL, ventrolateral thalamus; GPi, globus pallidus, internal segment; SNr, substantia nigra, pars reticulata; Nacc, nucleus accumbens (ventral striatum); vm-caud, ventromedial caudate; tail caud, tail of the caudate nucleus; V Put, ventral putamen; dl-CAUD, dorsolateral caudate; PUT, putamen; VTA, ventral tegmental area.

less affected (and thus less dopamine-depleted) than more dorsal regions (ie, of the caudate nucleus and putamen),[42] whereas short-term spatial memory was associated more readily with caudate dopamine function.[32]

Cools et al.[43,44] and Rowe et al.[45] subjected this hypothesis to further tests. Cools et al.[43] found that task-set switching, plausibly linked to fronto-executive functions recruiting the dorsal striatum,[46] was improved by dopaminergic medication, whereas they confirmed that probabilistic reversal learning was impaired. Furthermore, patients with PD also showed abnormal betting strategies on the Cambridge Gamble Task,[44] thus exhibiting greater impulsivity and delay aversion, consistent with the enhanced compulsive gambling after dopamine D2 receptor agonist medication that was being reported at that time.[47]

Cools et al.[43] proposed a *dopamine overdose* theory to account for these findings along the lines of the Yerkes-Dodson account proposed above (see also Rowe et al.[45]). A later study[48] purported to show some direct evidence for this in a functional magnetic resonance imaging (fMRI) study of patients with PD performing the probabilistic reversal learning task both *on* and *off* medication. They observed that the normal change in blood oxygenation level-dependent response that occurred in the vicinity of the nucleus accumbens (ventral striatum) during a reversal of task contingencies was apparently occluded when the patients were tested under L-dopa, thus corresponding to their failure to make the shift. The shift in blood oxygenation level-dependent response was reminiscent of a shift in phasic changes in firing defined by Schultz,[49] when recording from midbrain dopamine neurons in monkeys, as representing *prediction errors*, ie, mismatches between expected and obtained outcomes in the theoretical framework of reinforcement learning (see below). Specifically, reversal learning might well depend on phasic dips in dopamine, reflecting the surprising absence of expected reward. L-Dopa may have occluded these dips by enhancing local levels of tonic dopamine in the ventral striatum. Such a response would be less likely in the more severely depleted regions of the striatum associated with the motor symptoms of the disease. Given the apparently predictive relationships that prediction errors have with certain positive symptoms in schizophrenia such as delusions[50] and the purported role of mesolmbic dopamine in *aberrant salience*,[51] it is also possible that these *overdose* effects may be relevant to the understanding of some psychotic effects of dopamine medication in PD.[52]

The concept of a dopamine overdose in less depleted striatal regions was subsequently augmented by findings that a similar *overdosing* may occur in the PFC but via a completely different experimental approach. Foltynie et al.[53] observed that polymorphisms of the catechol-O-methyltransferase (*COMT*) gene associated with methionine (met)/met alleles in patients with PD exhibited greater cognitive impairment on the CANTAB Tower of London planning task compared either with valine (val)/val homozygotes or val/met heterozygotes. This was most surprising, because it was observed previously that healthy volunteers with val/val alleles had impaired working memory function, hypothetically because of a more *efficient* form of COMT that selectively depletes dopamine in the PFC due to the dependence of PFC dopamine for regulation on methylation rather than on re-uptake. The met/met alleles were associated with

enhanced prefrontal dopamine function because they control a less efficient form of COMT.[54] The impairments in patients with met/met alleles were associated with an increased response to L-dopa medication and were found more easily in men than in women. These findings perhaps can be explained most parsimoniously in the context of the PFC dopamine up-regulation that occurs in the earliest stages of PD,[55,56] prior to depletion at a later stage. Indeed, the pattern of results appears to be reversed when the same PD patients are tested several years later,[57] by which time the disease has become more severe; paradoxically, this may coincide with improved performance on the planning task, presumably because the PFC dopamine levels have reattained an optimal level in terms of the inverted-U-shaped curve of the hypothetical Yerkes-Dodson function. Such findings may well limit the usefulness of tolcapone-like COMT inhibitors and other dopaminergic medication in PD, as increasing dopamine levels in the PFC may well lead to greater cognitive impairment in patients with met/met alleles.

It should be noted that COMT is by no means the only likely modulator of fronto-executive function in PD. A polymorphism (brain-derived neurotrophic factor [*BDNF*] Val66Met) associated with BDNF (which is prominently implicated in the survival and functioning of midbrain dopamine neurons and in the regulation of dopamine D3 receptor) reportedly exerted a gender-specific influence on Tower of London planning in 291 patients with PD (overlapping heavily with the cohort used in the COMT studies).[58] Those patients with low rates of BDNF secretion, as a consequence of met alleles, performed significantly better than those with high rates. The effect was most apparent among women and among those patients with prior dopaminergic medication, consistent with previous evidence of interactive modulations of dopamine function by estrogen and BDNF that lead to relative dopamine hyperactivity in the PFC and consequent cognitive impairment. The effects of the COMT and BDNF polymorphisms within the same population of PD patients were additive and independent. Previous studies have indicated that this polymorphism is associated in healthy individuals with performance in episodic memory tasks.[59] Thus it is possible that this independence represents the influence of another neural system on planning performance, consistent with these patients recruiting hippocampal memory systems more readily than controls in performance of the task.[60] However, the BDNF Val66Met polymorphism has not been established to be an important influence in longitudinal studies of cognitive decline.[61]

## PD and Reinforcement Learning Theory

The possible link of PD with reinforcement learning has been exploited by several investigators. In an important study, Knowlton et al.[62] originally demonstrated that patients with PD had impaired trial-and-error learning on the *weather-forecasting* task, in which participants are required to learn which configuration of four visual cues best predicts sun or rain. Those authors interpreted this as an "implicit learning" deficit, contrasting with intact explicit memory of actually performing the task. Patients with medial temporal lobe lesions, by contrast, had no difficulty with learning on the weather-forecasting task but were impaired in their explicit memories. In fact, although the weather forecasting task clearly involves reinforcing feedback, its exact status within reinforcement learning theory is unclear (see Foerde and Shoramy[63]).

Within the category of reinforcement learning, an important distinction must be drawn between effects on goal-directed learning (often termed action-outcome learning) and stimulus-response habit learning, in that the latter does not require explicit representations of the outcome. Both of these forms of reinforcement learning depend on neural networks, including different sectors of the striatum (the caudate nucleus for goal-directed behavior and the putamen for stimulus-response habit learning; see Balleine and O'Doherty[64]), and it has been proposed that both depend on striatal dopamine as well as the PFC in humans[65,66] and in rats.[64,67] Indeed, although the weather-forecasting deficit was originally proposed to reflect a habit-learning deficit, more recent work suggests that PD (also or perhaps instead) is accompanied by impaired goal-directed control of learning.[68]

As mentioned previously, Lange et al.[20] had observed a tendency toward visual discrimination learning deficits that were remediated by L-dopa, but this occurred in patients with rather advanced disease. Impaired acquisition on various visual discriminations have subsequently been shown by a number of studies,[67-73] consistent with analyses based on neurocomputational models.[72-74] A particularly elegant series of studies was completed by Shohamy et al.,[75,76] who demonstrated that the deficit in learning visual associations was relatively specific, in that it depended on the receipt of reinforcing feedback. Patients who were required to learn the same associations by observation alone were no different from controls. This result was consistent with evidence of relatively unimpaired learning of visuospatial associations in the CANTAB paired associates learning task[13,22] (however, see Smittenaar et al.,[77] who observed impaired observational learning in patients with mild PD). In the latter studies, it was only patients with advanced PD who showed any impairments, in accordance with the viewpoint that some of these patients were exhibiting a progression to dementia.

Nevertheless, the nature of the reinforcement learning deficit and its underlying pathology was

complicated by several findings. Thus dopaminergic medication, in fact, did not appear to make much difference, and performance on a number of learning tasks was impaired regardless of whether patients were *on* or *off* medication.[69,72,78] Subsequent work has shown that the effects of PD (and dopaminergic medication in PD) on learning depend on the valence of the feedback, with opposite effects on learning from reward versus punishment. Although patients who were tested *off* medication appeared to learn more about the discriminative stimuli when they had received error feedback (punishment) than reward feedback, when they were tested *on* dopaminergic drugs, the patients exhibited the usual bias toward stimuli paired with reward.[79] This result conceivably could have explained the problems in reversal learning described by Cools et al.,[43] because the lack of medication enabled the patients to focus on the error feedback provided during reversal, whereas L-dopa may have promoted over-focusing on the rewarded elements, thus promoting perseveration. In terms of Frank's model,[79,80] poor learning in both unmedicated PD and medicated PD can also be explained in terms of abnormal dopamine levels. The model proposes that, in the unmedicated state, there is too little dopamine coding for reward, so that learning on the basis of positive feedback is impaired; and, in the medicated state, there is too much dopamine occluding the *dips* that normally signal reward absence, so that learning on the basis of negative feedback is impaired. The observation that PD did not alter performance on tasks that required learning from both reward and punishment, thus, might reflect a combination (and cancelling out of) these opposite effects. The key findings of beneficial effects of dopaminergic medication on reward-based learning and a detrimental effect on punishment learning have been replicated in several other studies[81-85] (although not in the study by Rutledge and colleagues[86]).

The precise interpretation of the apparent changes in reinforcement learning in PD is open to debate in the light of two recent studies suggesting that the effects of dopaminergic medication on reinforcement learning may be accompanied by performance effects consistent with motivational accounts of dopamine function. Thus both Smittenaar et al.[77] and Shiner et al.,[74] using variations of Frank's elegant associative learning procedure, have demonstrated that the effects of dopaminergic medication may become apparent, not just during acquisition of visual associations per se, but when the values of the discriminanda are manipulated in retention testing. For example, Smittenaar et al.[77] showed that dopaminergic medication potentiated a reward-based approach in terms of accuracy and reaction times in a group of patients with mild PD while leaving punishment-based avoidance unaffected. Thus, consistent with much animal literature (eg, see Berridge[87] and Robbins and Everitt[88]), dopamine appeared to affect incentive-motivational processes rather than, or perhaps in addition to, learning per se.[89] (However, note that this conclusion is not necessarily incompatible with Frank's computational modelling perspective.[80]) Such impairments are likely to be relevant to symptoms of apathy in PD (cf, Lawrence et al.[90]). The significance of such motivational impairments is that it is clearly difficult to interpret possible effects on learning when the expression of learning in performance is also affected (unless dopamine is experimentally manipulated *after* associative learning has occurred, as is feasible in animal experimentation[89]).

In a parallel experiment, Shiner et al.[74] tested patients in a two-stage reinforcement learning task while they were *on* and *off* dopamine replacement medication. Contrary to the authors' expectations, they found that dopaminergic drug state (*on* or *off*) did not impact learning. Again, the critical factor was drug state during the second, performance phase, with patients *on* medication choosing correctly significantly more frequently than those *off* medication. This effect was independent of drug state during initial learning and appeared to reflect facilitation of generalization for learned information. Those authors supported this conclusion by observing that neural activity in the nucleus accumbens and ventromedial PFC, measured during a simultaneously acquired fMRI paradigm, represented acquired stimulus values during performance. This effect was expressed only during the *on* state, when activity in those regions correlated with better performance, strengthening the proposal that positive effects of dopaminergic medication on reward learning in fact might reflect positive effects on the expression of such learning. Moreover, the locus of effects, particularly in the ventromedial PFC, is also consistent with the goal-directed nature of the deficit on such tasks, as demonstrated by de Wit et al.[65] (given the implication of this region in goal-directed action selection).[91] Therefore, the results suggested that dopamine modulation of the nucleus accumbens and the ventromedial PFC affected goal-directed choice rather than simply learning and may have been related to motivational effects or other performance factors. It might be noted that this observation is not necessarily inconsistent with the dopamine overdose hypothesis, according to which dopamine overdosing might be particularly (perhaps selectively) detrimental for learning from punishment rather than reward.[92]

The reinforcement learning approach is also somewhat compromised by several findings in the study by Swainson et al.[93] of patients with PD at different levels of disease progression (early, unmedicated; mild, medicated; severe, medicated later in the course) as well as

patients with Huntington' s disease and focal brain damage of the PFC and temporal lobe. That study examined (1) action-reward instrumental learning, in which eight pairs of unidimensional line stimuli were employed, one receiving rewarding feedback and the other receiving error feedback, presented in a successive, concurrent discrimination paradigm; and (2) because so many of the studies in the literature employ compound stimuli that have several perceptual features, a *five-dimensional* learning task also was employed in which pairs of visual stimulus objects (ie, compound stimuli) varied over five perceptual dimensions, including color, shape, position, etc. In that task, patients were required to find, by trial and error, the correct dimensional rule that best predicted rewarding feedback. Importantly, none of the basal ganglia groups were impaired in tasks the eight-pair, concurrent discrimination tasks, whereas the temporal lobe lesion group exhibited impaired learning. On the surface, this rather militates against the view that the basal ganglia play major roles in trial-and-error learning per se, but it is possible that a deficit in reward learning might have surfaced had the paradigm enabled a separate assessment of reward-and-punishment learning. To all intents and purposes, the clinical implications of this work are that patients with PD will be able to overcome practical difficulties in everyday learning of simple material if they are able to rely on multiple forms of feedback (ie, negative as well as positive).

However, there were major deficits in learning the five-dimension task in the medicated PD groups in the study by Swainson et al. Such effects have to be interpreted in terms of whether the patients were impaired in their perception of the stimuli or, alternatively, in terms of attentional selection (see also the review by Price et al.[94]). The impairment in the mildly medicated patients, in fact, was obscured by an apparent inability to identify the five dimensions perceptually before the task—presumably caused by L-dopa medication, because this effect was not observed in unmedicated patients with PD. This perceptual deficit also was not observed in the patients with more severe PD, who, thus, did exhibit a selective impairment in learning which dimension was relevant. This impairment was also observed both in the patients with cortical damage and in the patients with Huntington's disease. The lack of remediation by dopaminergic medication in the PD patients in this study does not argue strongly for a role for dopamine as distinct from other elements of cortico-striatal circuitry.

Another recent study[73] also argued against a major role for dopamine in the effects of PD on learning by more directly exploring the relationship between fronto-striatal gray matter atrophy and learning in PD. That study employed a discrimination learning task and computational modelling in order to assess learning rates in nondemented patients with PD. Behaviorally, learning rates were reduced in patients relative to controls. Voxel-based morphometry imaging analysis showed that this learning impairment was directly related to gray matter loss in discrete fronto-striatal regions (specifically, the ventromedial PFC, the inferior frontal gyrus, and the nucleus accumbens). Together, the findings suggest that PD is accompanied by deficits in both learning and the expression of learning. Critically, dopaminergic imbalance may not be the sole determinant of discrimination learning deficits in PD. These findings again highlight the importance of factoring in the broader pathological changes when constructing models of learning in PD.

Overall, the findings suggest that any role for striatal dopamine in the cognitive deficits of PD may be quite discrete, and perhaps the most consistent evidence for improvement remains the remediation of the spatial (short-term) working memory deficits. Dopamine may also improve reward-based learning in certain circumstances, especially when attentional selection is required, counteracting the consistently replicated tendency of patients with PD preferentially to use punishment-based learning. There are now as many examples suggesting that striatal dopamine may deleteriously affect certain functions, presumably in some sense because of *overdosing* either on a regional basis or in terms of extracellular levels at the synapse. The findings are theoretically important in terms of the functions of dopamine and the striatum; but, clearly, cognitive deficits in PD cannot inversely be inferred simply to reflect striatal dopamine depletion.

## Nondopaminergic and Nonstriatal Influences on Cognition in PD

Thus, there is strong evidence that striatal and PFC dopamine cannot be the only major factors in the cognitive profile presented by PD. However, there is also a clear dearth of evidence regarding which other neurotransmitters may be involved, despite indications of major changes in the systems of the isodendritic core, including noradrenergic, serotoninergic, and cholinergic ascending pathways[34-39] (Fig. 1). The serotoninergic changes more usually have been related to depression in PD rather than cognition,[95] although a recent study has shown beneficial effects of citalopram on response inhibition deficits in PD patients in a laboratory study.[96] The involvement of noradrenergic mechanisms is plausible in view of the early degeneration of the locus coeruleus in PD.[34] This has been supported recently by promising effects on cognition (rather than on depression) of the noradrenaline reuptake blocker atomoxetine in PD[97,98] and by more recent data (Kehagia et al, unpublished observations) indicating beneficial effects of this drug on *impulsive* features of PD as measured, for example, by

improvements on the stop-signal reaction time task. However, these beneficial effects are apparently limited by inverted-U shaped Yerkes-Dodson functions (Kehagia et al, unpublished observations).[99]

Another major neurotransmitter influence is via the cholinergic system,[35] with acetylcholinesterase activity, as measured by positron emission tomography, lower in patients who had PD with dementia (compared with patients who had nondemented PD and Alzheimer's disease) throughout the entire cortex and in particular in the frontal, parietal, and superior temporal cortices as well as the hippocampus.[39] Moreover, consistent with the detrimental effects of anti-cholinergic medication on visuospatial memory in early PD reviewed above, cholinesterase inhibitors such as rivastigmine are the most efficacious in conferring moderate clinical benefits in PD dementia, with beneficial effects on fluctuations in attention and visual hallucinations.[38,100] These effects are of considerable theoretical significance, as recent evidence suggests that PD dementia follows a course quite independent of dopamine-modulated fronto-striatal working memory and reinforcement learning functions.

## PD With Dementia: The Dual Syndrome Hypothesis

In addition to exhibiting some clear signs of fronto-striatal cognitive impairment, PD is associated with a clinical (cortical) dementia that is progressive and includes especially attentional, memory, spatial, and language deficits. Kehagia et al.[101] proposed a broad dichotomy between these hypothetically independent, although partially overlapping, syndromes of mild cognitive impairment and dementia in PD. One striking finding supporting this view was that drawing overlapping pentagons and verbal fluency (for the semantic category of animals) was markedly impaired and was more predictive of a diagnosis of clinical dementia than performance on a fronto-executive task such as the Tower of London.[102] These deficits are generally insensitive to dopaminergic medication and presumably (in the case of drawing and animal fluency) implicate posterior cortical dysfunction, including the parietal and temporal lobes. Therefore, it appears that, broadly, there are two main syndromes associated with cognitive deficits in PD: frontostriatal deficits that are modulated by dopamine, resulting in either performance enhancement or deficit; and a second, more posterior cortical syndrome that is reminiscent of such conditions as Lewy body dementia and perhaps dementia of the Alzheimer type. However, although Lewy bodies resulting from α-synucleopathies are pathognomic in PD,[40] there is also correlative evidence of tau body involvement in these cognitive deficits.[103] A major question arising from this hypothesis is the relative prevalence of cognitive deficits in PD, not only of PD dementia itself but also of the mild cognitive impairment (including the fronto-striatal deficits), and the relationship between them. One recent study, based on newly developed criteria for mild cognitive impairment in PD, has estimated that about 42.5% of new cases also present with *mild* impairment.[104] It is unclear, however, how many of these cases proceed to clinical dementia and what degree of overlap there is among these early deficits and the prevalence of dementia, estimated variously at between 24% and 31% of PD patients, with a much smaller proportion exhibiting the more specific form of PD dementia.[105]

## The Use of Longitudinal Cohort Studies to Characterize Cognitive Deficit Heterogeneity in PD

There has been a trend toward large cohort studies in PD, counterpointing the profusion of neuropsychological studies of smaller groups, carefully screened to exclude or minimize dementia or other confounding factors such as depression. Large cohort studies have systematically addressed cognitive heterogeneity in PD. Applying a community-based epidemiological approach to a population of approximately 700,000 over a 25-month incidence period, the "Cambridgeshire Parkinson's Incidence from General Practitioner to Neurologist" (CamPaIGN) study was perhaps the first to assess the incidence of PD and parkinsonism and the extent and natural history of cognitive deficits in the ensuing patient cohort.[106] Five subgroups of patients were identified in terms of disease presentation who were impaired on (1) the CANTAB Tower of London task, indicating fronto-striatal deficits[107,108]; (2) visual pattern recognition memory, indicating temporal lobe dysfunction[109]; (3) both the Tower of London task and visual recognition memory; (4) a cognitively preserved subgroup; and (5) a group of patients with marked cognitive impairment and a Mini-Mental State Examination score indicative of dementia.

Cluster analysis was used to separate patients into groups in order to infer the evolution of cognitive impairment,[57] identifying one cluster of patients with mild cognitive deficits and rapid disease progression and another cluster of cognitively impaired patients with a nontremor-dominant, akinetic motor phenotype at presentation with dopamine-unresponsive gait disturbance.[110] In fact, it was the CamPaIGN study that produced the striking finding mentioned above concerning PD dementia by identifying a patient phenotype indicative of early transition to this condition, which included older age (>72 years) at presentation and poor performance on two simple bedside tests of semantic fluency and copying overlapping pentagons from the Mini-Mental State Examination.[57,102]

Using a candidate gene approach, Goris et al.[103] found a robust association between the microtubule-

associated protein tau (*MAPT*) gene and the rate of dementia in the incident cohort at 3.5-year follow-up. In the CamPaIGN cohort at 5-year follow-up and in an additional cross-sectional prevalent cohort, Williams-Gray et al.[57] replicated the predictive utility of neuropsychological deficits in the form of pentagon copying and semantic fluency, reflecting temporal lobe function, but not phonemic fluency, that was sensitive to frontal lobe damage in dementia. By contrast, some of the *classic* deficits within the fronto-striatal cluster, for example, on Tower of London planning (ie, the CANTAB Stockings of Cambridge task), were not predictive of progression to dementia, suggesting at least two independent aspects of the cognitive deficit syndrome. The H1/H1 *MAPT* haplotype, but not *COMT*, was also shown independently to predict the onset of dementia.

In summary, the dual-syndrome hypothesis differentiates between two broad syndromes: (1) a profile of neuropsychological deficit in nondemented PD patients with *mild cognitive impairment* and a tremor-dominant phenotype on tests of planning, working memory, and executive function reflecting fronto-striatal dysfunction amenable to dopaminergic amelioration but susceptible to overdosing effects and modulated by the effects of *COMT* polymorphism and disease severity; and (2) an akinetic subgroup with pronounced gait disturbance demonstrating early deficits in visuospatial function and semantic fluency indicative of posterior cortical and temporal lobe dysfunction, in which patients exhibit rapid cognitive decline to dementia and in whom cholinergic treatment may offer some clinical benefit.[38] Nevertheless, some degree of overlap between the two *syndromes* seems likely given that nigrostriatal degeneration underlies the diagnosis of PD in the first instance and that any form of dementia with posterior cortical substrates is likely to be exacerbated by fronto-executive dysfunction.[101]

## Future Prospects for the Analysis and Treatment of Cognitive Deficits in PD: Genetic Influences on Cognition

The combination of better cognitive testing methods and their longitudinal application to large cohorts of patients with PD has meant that there is now much better understanding of the complexity as well as the importance of this significant class of symptoms. The heterogeneity of the deficits, however, and the multivariate nature of the underlying pathology continue to pose a major challenge for therapeutics. In addition to exploring drugs based on neurotransmitter actions, it will be necessary to investigate possible genetic underpinnings in order to develop new drug targets. This combination of cognitive neuroscience and genetics with longitudinal cohort approaches holds great promise more generally in terms of developing non-invasive methods that enable prediction of risk and treatment, not only of mild cognitive impairment and dementia but also of dopamine dysregulation/impulse control disorder, psychoses, and hallucinations and possibly of related disorders such as depression and sleep disturbances.

A related objective will be to investigate those factors that can predict future severe cognitive impairment in PD; from a state of *mild cognitive impairment*, perhaps to dementia. The Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation-(ICICLE) PD study represents an attempt to do this, also using potential dementia biomarkers that include Alzheimer's disease-like atrophy on structural MRI and lower levels of cerebrospinal fluid and β-amyloid 1-42.[104] Of particular promise may be the recent initiative to combine functional neuroimaging, genetic, and neuropsychological approaches, which may eventually be able to provide suitable biomarkers for the different elements of cognitive impairment. A pioneering study in this regard has been a further analysis of the COMT-related deficits in Tower of London performance in PD with a functional imaging paradigm, confirming the hypothesis that met/met patients exhibit a significantly reduced fronto-parietal activation that is normally associated with performance on this task.[111]

This finding has opened the way to using this methodology for more direct testing of the *dual-syndrome hypothesis* in two recent studies. The first of these is an analysis of the neurocognitive changes associated with the *MAPT* gene. Using fMRI to map cortical changes in activity during the encoding of visual memories, it was found that H1/HI homozygosity was associated with poorer memory recall in both patients (Winder-Rhodes et al, unpublished observations) with PD and age-matched controls. These memory impairments were associated with hypoactivation of the medial temporal lobe during memory encoding. However, some additional effects of *MAPT* on brain activation were found exclusively in PD patients; overall memory performance in *H1* homozygotes with PD showed a pronounced hypoactivation of the medial temporal lobes relative to *H2* carriers with PD; ie, this difference was only evident for patients with PD and not for the control group, regardless of genotype. This involvement of the medial temporal lobe in PD is consistent with the dual syndrome hypothesis. Another recent, unpublished study by Nombela et al went further by comparing influences of three polymorphisms in the same functional imaging study. An incident PD cohort (n = 169) and a matched control group (n = 85) were recruited to a neuroimaging study at two sites in the United Kingdom. All participants underwent clinical, neuropsychological, and fMRI assessments. The three neuroimaging tasks (Tower of London, spatial rotations, and

memory-encoding tasks) were designed to probe executive, visuospatial, and memory-encoding domains. Patients were also genotyped for three polymorphisms associated with cognitive change in PD and related disorders, namely: (1) rs4680 for the *COMT Val158Met* polymorphism, (2) rs9468 for *MAPT H1* versus *H2* haplotype, and (3) rs429358 for apolipoprotein-E-ϵ2,3,4 (*ApoE*). Cognitive performance deficits were determined in all three domains, each of which was associated with regionally specific changes in cortical activation. Task-specific, regional activations were linked with genetic variation: the rs4680 polymorphism modulated the effect of L-dopa therapy on planning-related activations in a fronto-parietal network, the *MAPT* haplotype modulated parietal activations associated with spatial rotations, and *ApoE* allelic variation influenced the magnitude of activation associated with memory encoding. The study established that neurocognitive deficits are common in patients with recently diagnosed PD, and the associated abnormalities of regional brain activations are influenced by genotype.

## Conclusions

This selective survey of research into the cognitive impairments associated with PD has revealed extraordinary advances over the past 30 years or so, from a position in which the very existence and nature of these deficits were disputed to one in which the deficits have become quite well characterized in terms of neural systems, chemical neuromodulation, and genetic influence, and the focus has turned to future therapeutic efforts, in line with the other, more traditionally recognized manifestations of this complex neurodegenerative disease. This work has shown that the traditional notion of PD as a model of striatal dopamine depletion in humans is oversimplified. Non-dopaminergic systems also are affected in PD (Fig. 1), consistent with the presence of dopamine-insensitive cognitive deficits. Large cohort studies with a data-driven approach have increased our understanding of the complexity of this disease and have given rise to the *dual-syndrome hypothesis*. ■

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