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Cognitive deficits in Parkinson's disease

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Abstract Neuropsychological investigations of patients with Parkinson's disease have shown specific impairments even in the early stages of the disease, which include deficit of behavioural regulation in sorting or planning tasks, defective use of memory stores, and impaired manipulation of internal representation of visuospatial stimuli. These deficits, reported in a disease which predominantly involves subcortical structures, have drawn attention to a potential role of the basal ganglia in cognitive processes. Given the modulatory role of the basal ganglia, these disorders might result from more fundamental deficits concerning the allocation of attentional resources, the temporal organization of behaviour, the maintenance of representations in working memory or the self-elaboration of internal strategies, all of which resemble dysfunctions of processes that are commonly considered to be controlled by the frontal lobes. This suggests a functional continuity or complementarity between the basal ganglia and association areas of the prefrontal cortex. The recent description in primates of segregated loops that interconnect discrete regions of the caudate nucleus to the dorsolateral and orbitofrontal regions of the prefrontal cortex via the thalamus may give some support to this hypothesis. Alternatively, degeneration of the ascending cholinergic and catecholaminergic neuronal systems may contribute, at least in part, to the occurrence of this frontal-lobe-like symptomatology associated with Parkinson's disease.

Key words Parkinson's disease · Cognitive deficits · Executive functions · Dementia · Dopaminergic systems

Introduction

Several cognitive deficits can be observed in non-demented patients with Parkinson's disease (PD), even at the early stages of the disease, if one uses appropriate neuropsychological tests. They mainly include defective use of memory stores and a dysexecutive syndrome. These disorders result from dysfunction of processes that are commonly considered to be controlled by the prefrontal cortex. In contrast, a more global impairment is far less frequent and, in this latter case, the role of histological changes of cortical neurons, such as the neurofibrillary tangles or the Lewy body inclusions, is a matter of debate.

Which are the specific cognitive changes in PD?

Cognitive deficits are observed very frequently in PD; 93% of the patients compared with matched controls were shown to be impaired in one study [66]. These deficits may be related to the subcortical pathology of the disease, because they are noticed even at an early stage, at a time when the lesions are considered to be restricted to the ni-

grostriatal dopaminergic pathway [1]. They mainly affect visuospatial functioning, memory and executive functions.

There is considerable evidence of *visuospatial dysfunction* in PD, even when intellectual efficiency is preserved and tests require few motor components [6, 8, 35, 40]. Although some authors believe that there is a genuine visuospatial deficit in PD, most attribute impaired performance to the high cognitive demand usually required by these tasks. Indeed, except for difficulties in discriminating line orientation, the deficits are only observed in paradigms requiring set-shifting [13, 69], self-elaboration of the response [68] or forward planning capacity [55]. In a study using both visuospatial and frontal-related tasks, visuospatial deficits disappeared once performance on the frontal-related tasks was statistically covaried [7]. Therefore, visuospatial disorders in PD result more from a decrease in central processing resources than from a specific alteration of visuospatial function.

Several memory functions are impaired in PD. *Working memory* capacity is decreased, as shown by defective short-term recall in tasks requiring: the inhibition of interfering stimuli, such as the Sternberg paradigm [84] or the Brown and Peterson procedure [16, 49]; digit ordering [18]; or spatial organization [10, 56]. *Long-term memory* may be impaired as well, depending on the nature of the task and the processes that are required. For instance, the slope of the learning curves is normal in PD patients and there is no loss of information after a delay. These results indicate that the storing and consolidating processes that are under the control of the temporal lobes tend to be preserved in the disease [65]. In contrast, the performance of PD patients in explicit memory tests is significantly decreased in those tasks which require organization of the to-be-remembered material [15, 79, 80], temporal ordering [70, 83], or conditional associative learning [72]. Thus, internal control of attention, required to generate spontaneously efficient encoding and retrieval strategies, is impaired in PD. There is also some evidence that *procedural learning* may be decreased. For example, non-demented PD patients were found to be impaired in rotor pursuit [32], on the serial reaction time task [26, 59], on mirror reading (Sarazin, Deweer et al., in preparation), and on the Tower of Toronto [71]. Patients are not unable to acquire motor or mental sets, but have difficulty in maintaining new acquired sets against competing alternatives, suggesting again a deficit of internal control of attention.

Executive functions are also altered in PD. This cognitive domain refers to the mental processes needed for the elaboration of adaptative behaviour in response to new challenging environmental situations that include the processing of relevant information, the generation of new concepts or mental sets, problem-solving and planning abilities. All these processes are known to be disturbed after damage to the frontal lobes. They can be investigated with several kinds of tasks which all require cognitive flexibility or internally guided behaviour: (1) Wisconsin Card Sorting Test and delayed response tasks for concept formation and rule-finding; (2) Trail Making and Odd Man Out Tests for set-shifting; (3) Letter fluency and Stroop test for set-maintenance; (4) Tower tasks for problem solving. All these tasks, considered as specifically sensitive to frontal lobe lesions [77], are disturbed in PD [25].

Beside the apparent diversity of cognitive disorders in non-demented patients, there is now a trend to consider that they may result from some fundamental dysfunction, the nature of which remains debated: a deficit in behavioural control and regulation [9] responsible for the difficulty to shift or maintain mental sets; an inability to elaborate internally guided behaviour [79], which may account for problem-solving and recall deficits; a decrease in processing resources and internal control of attention [14], which penalizes PD patients in tasks which are heavily loaded in cognitive demand. Whatever the relevance and validity of these hypotheses, they all implicate processes that are under frontal lobe control. If so, the basal ganglia and the prefrontal cortex may share a complementary role in these functions, as shown by a careful analysis of the patients' performance. For instance, if patients with frontal lobe lesions [53] and patients with PD [9, 79] both have difficulty in achieving criteria on the Wisconsin Card Sorting Test, the number of perseverative responses is only increased in patients with frontal lobe lesions. In contrast, PD patients have more difficulty in maintaining a response set for a new relevant dimension than in disengaging their attention from a previously reinforced category [57, 58]. Here again, the role of the striatum in the maintenance of mental set, already suggested from procedural learning studies, is highlighted. Another specific function of the striatum may be related to sensory integration, since PD patients are impaired in the discrimination of two sensory stimuli [5], suggesting that the striatum would intervene in focusing attention on a single event while "suppressing" all others, as postulated by Hassler [33].

Which might be the pathophysiological mechanisms of specific cognitive changes in PD?

It is well known that degeneration of nigrostriatal dopaminergic neurons is the major lesion in PD, as reported post mortem [1] and demonstrated in vivo by PET studies using ^{18}F-6-fluoro-L-dopa [11, 41]. Indeed, clinical and experimental observations implicate dopaminergic transmission in some aspects of cognitive impairment. Firstly, intoxication by 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydopyridine (MPTP), a drug which selectively destroys the nigrostriatal dopaminergic neurons, interferes with planning and internal control both in animals after experimental injection [81] and humans after accidental administration

[74]. Secondly, cognitive difficulties have been shown in newly diagnosed and not yet treated de novo PD patients, particularly in tasks requiring internal control of attention, complex visuospatial perception and recent memory [17, 42, 43]. Thirdly, a beneficial influence of levodopa therapy on cognition has been observed in non-demented PD patients, particularly in choice reaction time tasks [67], in a verbal working memory test of digit ordering [18] and in a visuospatial working memory test [39], all tasks sensitive to internal control of attentional resources and frontal-lobe like functions. In a recent study, the ability to process simultaneously two cognitive tasks was significantly impaired in patients who were in a state of striatal dopaminergic depletion after withdrawal of levodopa therapy [46]. The experimental procedure consisted of the following tasks: a visual choice reaction time task with squares of different colours appearing on a screen and a right-hand response to the red square; and an auditory choice reaction time task with high- or low-frequency sounds and a left-hand response to the high-frequency tone. The tasks were presented first separately, and then simultaneously. In the simultaneous condition, the inter-response interval – the time difference between the first and the second response – reflects the ability to process concurrent information in parallel. Compared with controls, treated PD patients performed normally. By contrast, de novo patients had a significantly longer inter-response interval, although they had a shorter disease duration than the treated PD group (1.7, SD 0.3 versus 8.1, SD 1.1 years). The same increase in inter-response interval was also observed in standard PD patients assessed in the "off" state, after a short withdrawal of levodopa treatment, compared with their performance in the "on" state, at maximum effect of treatment. These results illustrate the role of dopaminergic transmission in the modulation of information processing.

How may the nigrostriatal dysfunction that characterizes PD interfere with frontal lobe functions? A recent description of the striatofrontal circuits of primates may provide a coherent explanation [3]. Five independent, parallel, and recurrent loops have been postulated, each of which interconnects specific areas of the prefrontal cortex to restricted, well-defined subregions of the basal ganglia. The functional role of these striatofrontal circuits is more or less established for the "motor" and "oculomotor" loops. Such is not the case, however, for the three remaining circuits, which are consequently labelled as a function of their cortical areas: "dorsolateral", "orbitofrontal" and "anterior cingulate". Given their cortical targets, it is reasonable to assume that these loops are involved in complex cognitive, behavioural or motivational functions. Thus, the frontal dysfunction observed in nondemented PD patients may result from disruption of the complex loops either at the level of the striatum, resulting from a lesion of the nigrostriatal dopaminergic pathway, or at the level of their cortical target, resulting from a lesion of the mesocortical dopaminergic system [1].

The dopamine hypothesis is attractive because it takes into account the most severe lesion reported in PD. It remains to be explained, however, why the restoration of central dopaminergic transmission with levodopa treatment does not improve the cognitive changes to the same extent as the dopamine-dependent motor signs. This may be interpreted in two ways: (1) cognitive changes are mediated by a dopaminergic mechanism, but are unresponsive to levodopa for pharmacodynamic reasons that are not yet understood; (2) cognitive changes are mediated, at least in part, by lesions of nondopaminergic neuronal systems; in these situations, levodopa would not be expected to be fully effective. Indeed, patients become increasingly handicapped during the course of the disease by symptoms such as gait disorders, dysarthria or cognitive deficits that are unresponsive to levodopa and are therefore considered to result from non-dopaminergic lesions of the brain [61]. These symptoms may be the consequence of the progressive degeneration of other ascending neuronal systems, i.e. cholinergic, noradrenergic and serotonic systems, that have been reported post mortem [21]. Interestingly, each of these ascending systems has been shown, on the basis of pharmacological, pathological or experimental evidence, to have an effect on cognition. For example, blocking cholinergic transmission with anticholinergic drugs consistently results in learning and frontal lobe type deficits in patients with PD [23]. Experimental lesions of the locus coeruleus, the site of origin of cortical and limbic noradrenergic innervation, reduce selective attention and learning in animals and may contribute to cognitive slowing in PD patients [75]. Age of onset of the disease is also an important factor to take into account, because it may influence the threshold at which neuronal lesions become symptomatic. Indeed, the compounding effect of ageing on cognition has been demonstrated by comparing the neuropsychological performance of early-onset and late-onset PD patients with that of age-matched controls [24]. This compounding effect of ageing might account for the high frequency of cognitive disorders and dementia in PD patients whose disease begins later in life [44, 86].

How frequent is dementia in PD?

Before answering this question, it is important to recall that dementia in PD may be difficult to recognize. Firstly, DSM IV criteria [4] are well adapted for the diagnosis of dementia in Alzheimer's disease, but less appropriate for PD, where the severe motor deficits may intervene in the autonomy of the patient. Secondly, current test batteries do not include the assessment of executive functions, which is crucial not only to demonstrate the progressive cognitive decline in these patients, but also to distinguish the dementia of PD from that of other neurodegenerative diseases with movement disorders [64]. Thirdly, overesti-

mation of cognitive impairment may result from nonspecific factors, which interfere with the evaluation of cognitive functions. When "off" (at the minimal effect of levodopa treatment), patients can be severely akinetic with motor and cognitive slowing, hypophonic and slurred speech and anxiety, all factors that may affect the cognitive evaluation. When "on" (at the maximal effect of levodopa treatment), patients may be inattentive and hampered by uncontrolled dyskinesias. Depression, which is observed in about 50% of PD patients, is also an important factor to control, as it has been shown that beyond a certain depression threshold it may induce attention and memory disorders and mainly impair those cognitive functions that are in relation with frontal lobe function [73]. Anticholinergics may provoke an acute confusional state [20] or permanent more subtle cognitive changes [23], especially when patients are old and present memory disorders, both conditions in which the ascending cholinergic system is likely to be more severely damaged [22].

Dementia, however, is not infrequent in PD. It is generally considered that dementia occurs in about 15–20% of patients [12, 62, 78]. In an epidemiological study of 339 consecutive patients [52], the overall prevalence was 10.9%. This is likely to be an underestimation due to the shorter life expectancy in demented PD patients [47]. The risk of dementia in non-demented PD patients would be about twice that of age-matched non-demented elderly controls [48].

Which are the characteristics of dementia in PD?

If one refers to DSM IV criteria [4] dementia in PD patients may be described as a progressive dysexecutive syndrome with memory deficits, in the absence of aphasia, apraxia or agnosia. In these patients, the loss of intellectual efficiency can be evaluated by psychometric criteria, using a global scale such as the Mattis Dementia Rating Scale [51], which is more appropriate than the Mini-Mental State of Folstein et al. [27] for predominantly subcortical degenerative diseases, because it includes tests assessing attention and executive functions. Such tools provide cut-off scores that permit a psychometric approach of dementia and a distinction between demented and non-demented patients.

A deficit in learning new information, considered to be the hallmark for the diagnosis of dementia, has been reported in demented PD patients using the Wechsler Memory Scale or word list learning. It is, however, less severe than in Alzheimer's disease [34, 63, 76]. In a recent study, explicit memory was assessed using the Grober and Buschke procedure [30], which controls for the effective encoding of verbal items. Although demented PD patients exhibited a marked deficit in free recall, their performance was dramatically improved by semantic cueing, which triggered efficient retrieval processes [63]. This result suggests that recall deficit is not primarily due to a memory disruption since the ability to register, store and consolidate information is preserved, but rather to difficulties in activating the neuronal processes involved in the functional use of memory stores. Correlation analysis showed that the memory scores in this task were strongly related to performance on tests of executive functions, favouring the role of frontal lobe dysfunction in the defective activation of memory processes. The existence of a dysexecutive syndrome in PD patients with dementia, although less severe than in progressive supranuclear palsy [45, 62], is in agreement with this interpretation.

If this dysexecutive syndrome is the main characteristic of dementia in PD, instrumental activities are rather preserved. Linguistic difficulties, however, have been described in these patients. They include word-finding difficulties, decreased information content of spontaneous speech, diminished word list generation, impaired strategies in sentence comprehension [19, 50]. Moreover, poor performance on tests of verbal fluency would be a predictor of dementia in PD [37]. Praxic disorders may also be observed, although their nature is still a matter of debate [29, 31]. In any case, these instrumental deficits are less severe than in Alzheimer's disease [19, 36] and might be related to frontal lobe dysfunction [31]. As underlined by Girotti et al. [28], the cognitive deficits are more severe and widespread in demented than in non-demented PD patients, but affect particularly those tests that already discriminated non-demented patients from controls.

Which might be the pathophysiological mechanisms of dementia in PD?

The "subcortico-frontal" type of dementia demonstrated by neuropsychological studies leads to the hypothesis that cognitive disorders of demented PD patients result mainly from lesions of subcortical origin and that cognitive programs intrinsic to the cortex are not necessarily damaged but rather deactivated. Dementia may occur when damage of several ascending neuronal pathways reaches the necessary threshold required for the expression of severe cognitive impairment [2]. These dopaminergic, cholinergic, noradrenergic and serotoninergic neuronal systems contribute in parallel or by mutual interaction to the expression of integrated behaviours, as demonstrated in experimental studies. For example, the simultaneous disruption of the nigrostriatal and mesocorticolimbic dopaminergic systems causes marked impairment of the conditioned avoidance response in rats, whereas the selective disruption of one or the other of these systems has no effect [38]. It has been also shown that destruction of the ascending cholinergic system increases the behavioural consequences of damage to serotoninergic neurons [54].

Cortical changes cannot be ignored, however. Cortical neuronal loss, Alzheimer's-like histological changes, and

Lewy bodies in neurons of the cerebral cortex may play a crucial role in the intellectual deterioration, in addition to subcortical lesions. Indeed, there is a high frequency of Alzheimer's changes in the cerebral cortex of PD patients [60], but that is not correlated with dementia. A high level of abnormal tau proteins is detected in temporal and prefrontal cortices of demented PD patients [82], although the pattern and intensity of immunostaining differ from that observed in Alzheimer's disease. The role of cortical lesions is therefore not clearly established. Some cases of dementia have been reported in PD in the absence of apparent cortical lesions [22, 85], suggesting that subcortical lesions may be sufficiently severe to cause overt dementia, at least in some patients. Thus, the respective role of the two groups of lesions (cortical and subcortical) remains to be determined. Whatever the contribution of the cortical lesions, it should be kept in mind that the subcortical lesions may be solely responsible for the frontal-lobe like dysfunction and the inefficient activation of memory processes observed in PD patients, even in those who are demented.

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