Arq Neuropsiquiatr 2008;66(2-A):147-151

WORKING MEMORY IN PARKINSON´S DISEASE PATIENTS

Clinical features and response to levodopa

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Abstract – **Objective:** To evaluate the clinical features of the working memory (WM) in Parkinson's disease (PD) patients and to test the effect of levodopa on WM. **Method:** The paradigm was based on the 'n-back' tasks, which enables to study the level of executive demand (three levels of difficulty) and the domain of the information being processed (spatial items, faces and letters). The effect of levodopa was studied by testing PD patients in "on" and "off" states. **Results:** PD patients performed less well in WM tasks than controls. There was no interaction between groups and complexity. Levodopa therapy had a positive effect only on spatial WM tasks but no effect on complexity. **Conclusion:** Our results suggest that impairment observed may result from a maintenance deficit within WM regardless the level of processing and levodopa therapy presents a positive effect on spatial WM.

KEY WORDS: Parkinson's disease, striatum, executive functions, working memory, levodopa.

Memória de trabalho em pacientes com doença de Parkinson: características clínicas e resposta a levodopa

Resumo – **Objetivo:** Avaliar as características clínicas da memória de trabalho (MT) em pacientes com doença de Parkinson (DP) e testar o efeito da levodopa na MT. **Método:** O paradigma baseou-se nas tarefas 'n-back', que permitem avaliar o nível de demanda executiva (três níveis de dificuldade) e o domínio da informação sendo processado (posições espaciais, faces e letras). O efeito da levodopa foi estudado pela testagem dos pacientes no estado "on" e "off". **Resultados:** Pacientes com DP apresentam desempenho inferior ao dos controles em tarefas de MT. Não foi observada interação entre grupos e complexidade. A terapia com levodopa mostrou efeito positivo sobre a modalidade espacial, e nenhum efeito sobre a complexidade. **Conclusão:** Nossos resultados sugerem que o comprometimento observado pode resultar de défict de manutenção da MT, independente do nível de processamento. A terapia com levodopa apresenta efeito positivo sobre a MT espacial.

PALAVRAS-CHAVE: doença de Parkinson, striatum, funções executivas, memória de trabalho, levodopa.

Parkinson's disease (PD) patients present cognitive impairment affecting executive functions, such as planning ability, mental flexibility and activation of strategic processes[1]. At an anatomical level, this executive impairment results at least partly from a dysfunction of the caudate nucleus-prefrontal cortex (PFC) loops[2,3], as a consequence of the loss of dopaminergic inputs to the caudate nuclei and the PFC. At a cognitive level, the impairment of executive functions may be partly due to an alteration of working memory (WM)- a system that temporarily stores and manipulates information needed for complex cognitive tasks such as language comprehension, planning or reasoning[4]. Despite studies having reported WM impairment in PD patients[1,3,5-8], some issues remain to be determined: 1) It is unclear whether this deficit is caused by a dysfunction of the more executive aspects of WM, regardless of the nature of the information, or a storage impairment (i.e., the inability to maintain information in short-term memory)[6,8,9]. 2) The effect of levodopa therapy on WM performance remains to be clarified. A few studies have reported a beneficial impact of this agent on certain aspects of frontal lobe-related functions[10,11], including short-term and WM[12,13].

The aims of the present study were to assess the existence of WM deficit in PD, to determine if such deficits are associated with the capacity to maintain information

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Received 5 November 2007, received in final form 14 February 2008. Accepted 4 March 2008.

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in short-term memory or the nature of the information being processed in WM and to evaluate the effect of dopaminergic therapy over WM.

METHOD

General procedure

We studied the performance of PD patients and control subjects in several WM tasks ('n-back' tasks) varying in terms of complexity (mental manipulation and allocation of attentional resources) and domain (spatial items, faces and letters). Subjects were required to perform nine WM tasks: 1-, 2- and 3-back tasks for each type of material, i.e., spatial items, face and letter stimuli. Within each domain, the 1-, 2- and 3-back tasks were performed consecutively. The order of the three modalities was counterbalanced from one subject to another in each group (PD patients and control subjects). Control subjects performed the n-back tasks once. PD patients performed the tasks twice, once in the 'on' state and once in the practically defined 'off' state (after a 12-hour withdrawal of dopaminergic medication)[14]. In the PD group, the order of testing for the 'on' and 'off' conditions was randomized. Different sequences were used in 'on' and 'off' testing in order to avoid a re-test effect. We compared the results of PD patients in the 'on' and 'off' states and compared the results of the PD group and control subjects matched for age and education. Informed consent was obtained from all patients and control subjects. The study was approved by the Ethics Committee for Biomedical Research of the Salpêtrière Hospital.

Experimental tasks

Tasks were based on the n-back procedure[15], in which the subject has to indicate whether a visual stimulus presented on the screen (the 'target' stimulus) is similar to or different from a previously presented stimulus (the 'cue' stimulus). This procedure requires the relevant information to be maintained and updated in WM. Two dimensions were explored: 1) the level of mental manipulation within WM, with three different levels: 1-back (maintenance of one item of information in WM in the interval between the cue and target stimuli), 2- and 3-back (interposition of one or two 'distractors', respectively, between the cue and target stimuli, each 'distractor' becoming the cue for the next trial); 2) the nature of the stimuli being processed, with three different materials: different locations of squares on a matrix of several squares (the 'spatial n-back' task), different preselected men's faces (the 'face n-back' task) and different preselected letters (the 'letter n-back' task). In the spatial n-back task, the visual stimulus was a blue square presented randomly in one of six possible locations on a dark screen. In the face n-back task, the stimulus was a man's face among eight possible faces. These faces were chosen from Warrington's Recognition Memory Test for Faces[16]. In the letter n-back task, the stimulus was a capital letter among seven possible letters selected for their frequency of occurrence. Faces and letters were presented in a central position on the screen. The number of stimuli in each domain was the number that, in a pilot study involving 10 healthy controls, produced matched performances.

All tasks were computerized and started at a 'go signal' triggered by one of us (RB), who stood behind the subject throughout the testing procedure. Participants were seated in front of a personal computer screen. Each n-back task started with the first cue stimulus (a square, a man's face or a letter) being presented on the screen for 3000 ms. The subject had three seconds to answer 'same' or 'different'. After a 1000-ms inter-stimulus interval, a new stimulus appeared on the screen. Each task consisted of two blocks of 15 responses to cue/target stimuli (16, 17 and 18 stimuli were presented in the 1, 2 and 3-back tasks, respectively). Responses were given orally. The total duration of one session was about 50 minutes.

Subjects

Eighteen patients with idiopathic PD according to the United Kingdom brain bank criteria[17] participated in this study. All were in-patients in neurological departments at Salpêtrière Hospital. Exclusion criteria were (i) parkinsonian syndromes resulting from the administration of anti-dopaminergic drugs or other neurodegenerative diseases; (ii) the presence of dementia, defined as a score <130 on the Mattis Dementia Rating Scale[18], or depression, defined as a score >18 on the Montgomery and Asberg Depression Rating Scale[19]; (iii) treatment with anticholinergics; and (iv) severe 'on' dyskinesias that could interfere with the level of attention required to perform the tasks.

There were 11 men and seven women, aged from 45 to 73 years (mean±SD=52.7±7.7). Years of education ranged from 8 to 16 (mean±SD=13.8±2.7). Mean duration of the disease was 11.6±4.8 years. At the time of testing, the severity of the disease was assessed with the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS)[20]: mean 'on' score±SD=14.5±9.2; mean 'off' score±SD=37.6±11.6, and the Hoehn and Yahr scale[21]: three patients at stage II, 12 at stage III, and three at stage IV; mean score±SD=3.0±0.6. All patients were receiving chronic levodopa treatment and 16 of them also received dopaminergic agonists. The mean daily levodopa dose (levodopa and levodopa equivalent) was 902±434 mg. In all patients, levodopa responsiveness was considered good (62.2% improvement on the motor part of the UPDRS between the 'on' and 'off' states), leading to motor fluctuations in every patient. Other psychotropic drugs taken were as follows: COMT inhibitors (n=4), benzodiazepines (n=3) and antidepressants (n=5). A neuropsychological evaluation was systematically performed in PD patients (Table 1). Cognitive abilities were preserved; particularly there was no impairment of executive functions. Their performance was compared to that of a group of 21 control subjects matched for age and years of education. All of the control subjects were community volunteers in good health (based on self-report) with an MMSE score >26. None had a history of neurological or psychiatric disease.

Statistical analyses

We analyzed the proportion of correct answers in each condition. To stabilize variance, an arcsine of the square root of the proportion was applied. On these transformed data we per-

Table 1. Neuropsychological characteristics of PD patients.

	Performance	Pathological score
Mattis Dementia Rating Scale	139.2±3.6	<136
Wisconsin Card Sorting Test		
Criteria	5.7±0.7	<5
Perseverative responses	1.7±2.3	>2
Abandons	1.3±1.4	>2
Category fluency ('Animals')	20.9±7.5	<16
Literal fluency ('M')	11.7±3.9	<10
Grober and Buschke Test		
Free recall	25.4±5.3	<24
Total recall	46.9±1.6	<40
Montgomery and Asberg DRS	9.7±3.7	>18

Values are expressed as mean±SD.

formed four different ANOVAs: 1) in controls, we analyzed the effects of complexity and domain and a possible interaction between these two factors; 2) we compared PD patients in the 'off' state and in the 'on' state to controls to assess the group effect and its possible influence on complexity, domain and first and second order interaction between factors; 3) in PD patients, we compared the 'on' and 'off' states by repeated measures (ANOVA with patients as random effect) to assess the effect of levodopa and its possible influence on complexity, domain and first and second order interaction between factors. For significant factors or interactions, pair-wise comparisons were made with Tukey-Kramer adjustment for multiple comparisons (corrected *P* values (*P*c) are indicated in the text). The influence of other variables (age, gender, years of education) was analyzed in controls using ANOVAs. *P* values less than 0.05 were considered statistically significant. Statistical analyses were performed using the SAS 8.1 statistical package (SAS Institute, Cary, NC, USA).

RESULTS

Control subjects

A within-group ANOVA (1-, 2-, 3-back and three categories of stimuli) showed: (i) an effect of complexity [F(2,180)=231.76; *P*<0.0001], with an increase in the number of errors with complexity (1-back differed from 2-back [*P*c<0.0001] and 3-back [*P*c<0.0001], 2-back differed from 3-back [*P*c<0.0001]); (ii) an effect of domain [F(2,180)=4.71; *P*<0.02], with a greater number of errors for faces than for spatial stimuli (*P*c<0.008); (iii) no interaction between complexity and domain [F(4,180)=2.13; *P*=0.07]; (iv) and no influence of age, years of education or gender on performance.

PD patients in the 'off'state versus controls (Table 2)

A between-group ANOVA (1-, 2- and 3-back and three categories of stimuli) showed: (i) a group effect [F(1,333)= 45.82; *P*<0.0001]; (ii) a complexity effect [F(2,333)=365.23; *P*<0.0001]; (iii) no domain effect [F(2,333)=0.56; *P*=non significant (NS)]; (iv) no interaction between group and complexity [F(2,333)=0.77; *P*=NS], or between group, complexity and domain [F(4,333)=1.54; *P*=NS]; (v) an interaction between group and domain [F(2,333)=5.34; *P*<0.006]. Multiple comparisons showed a significant difference between the two groups on the spatial (*P*c<0.0001) and letter (*P*c<0.0001) tasks but not on the faces task. There was no influence of age, years of education or gender on performance.

PD patients in the 'on' state versus controls (Table 2)

A between-group ANOVA (1-, 2- and 3-back and three categories of stimuli) showed: (i) a group effect [F(1,333)= 23.93; *P*<0.0001]; (ii) a complexity effect [F(2,333)=398.70; *P*<0.0001]; (iii) a domain effect [F(2,333)=7.53; *P*=0.0006]; (iv) no interaction between group and complexity [F(2,333)=1.40; *P*=NS], group and domain [F(2,333)=0,81; *P*=NS] or group, complexity and domain [F(4,333)=0.15; *P*=NS]. There was no influence of age, years of education or gender on performance.

'On' versus "'off' state in PD patients (Table 2)

A within-group analysis with repeated measures (1-, 2-, 3-back, three categories of stimuli and two levodopa states) showed: (i) no effect of levodopa [F(1,305)=3.09; *P*= NS]; (ii) no interaction between levodopa state and complexity [F(2,305)=0.14; *P*=NS] or between levodopa state, complexity and domain [F(4,305)=0.92; *P*=NS]; (iii) but an interaction between levodopa state and domain [F(2,305)= 3.58; *P*<0.03] since there was a significant difference between the two states in the spatial task (*P*c<0.0001) – with improvement under levodopa – but not in the letter or the faces tasks. There was no influence of age, years of education or gender on performance.

Table 2. Performance of control subjects and PD patients in working memory tasks.

	Controls	PD patients	
		L-Dopa "off"	L-Dopa "on"
Spatial 1-back	29.97±0.15	28.78±1.00	29.83±0.38
Spatial 2-back	28.10±2.26	26.06±3.11	27.06±3.11
Spatial 3-back	22.63±3.42	20.11±3.08	21.11±3.39
Faces 1-back	29.59±0.62	29.44±0.92	29.17±1.20
Faces 2-back	26.29±2.81	24.89±4.43	25.06±3.54
Faces 3-back	23.02±2.38	21.94±3.42	21.00±3.40
Letters 1-back	29.78±0.74	29.39±1.33	29.44±0.98
Letters 2-back	27.37±2.34	24.17±4.37	25.00±4.04
Letters 3-back	23.17±2.42	18.50±3.13	19.89±3.41

Absolute values are expressed as mean±SD.

DISCUSSION

This study found that PD patients had significantly lower scores in the n-back tasks than matched healthy control subjects. This impairment persisted even when patients were receiving levodopa treatment (i.e. in the 'on' state). The lower performances in these tasks as compared to those of the control subjects are consistent with several studies reporting WM deficit in PD[1,3,5-8]. By modifying the n-back procedure, it was possible to study the impact of the level of complexity of processing (which differed between the 1-, 2- and 3-back tasks) and different domains of information (spatial, verbal or face). Our results in the 'off' state indicate that the WM deficit was not only restricted to the spatial domain but also affected the letter n-back task (where letters were sequentially presented in a central location). This result differs, however, from others reports showing a WM deficit restricted to the spatial domain in PD patients[8]. Our findings also show that the deficit in the n-back tasks in patients in the 'on' state was unrelated to the complexity or the domain of the tasks since no interaction between groups and complexity or between groups and domain was observed. The findings in the PD patients investigated in the present study were not related to disease parameters (i.e., age at disease onset, duration of the disease, severity of motor impairment). Neither were they accounted for by age, educational level, cognition or mood.

One might hypothesize that this global n-back task deficit found in our PD patients resulted from a non-specific impairment of executive functions, in particular of strategic and attentional processes, as previously suggested[7]. This hypothesis, however, is weakened by the finding that the patients herein studied had an excellent performance in executive function tests. It may be assumed, thus, that the impairment in the n-back tasks in PD patients reflects a WM deficit. Such impairment, also found by others[1,3,5-8] may be due to difficulty in maintaining information in short-term memory, regardless of the nature of the information being processed or the level of processing. This hypothesis is supported by the results of another study showing a WM impairment in PD patients performing a spatial delayed response paradigm, in which subjects were only required to maintain one spatial location during the delay period[22]. In addition, a maintenance deficit in short-term memory may also account for the pattern of impairment observed in PD patients performing the Wisconsin Card Sorting Task[23]. Indeed, PD patients can normally generate rules of sorting and shift from one rule to another. By contrast, once they have generated a strategy they have difficulty in maintaining it throughout trials.

Nigrostriatal denervation may contribute to WM impairment through a dysfunction of the fronto-striatal loops, in particular the pathways connecting the dorsolateral prefrontal cortex (DLPFC; BA 9/46) to the dorsal caudate nucleus[2]. However, striatal dopamine depletion alone is unlikely to be sufficient to explain the WM deficit since the restoration of striatal dopamine ('on' state) was not able to improve WM performance overall. In addition, lesion of the meso-cortico-limbic pathway[24] may produce a DLPFC dysfunction through prefrontal dopaminergic depletion. Indeed, changes in the prefrontal concentration of dopamine may significantly influence WM functions, as demonstrated in non-human primates[25]. Furthermore, in PD, noradrenergic, serotoninergic and cholinergic systems are affected as the disease evolves[26]. These ascending neuronal systems could disrupt WM through an arousal/attentional deficit[27] and consequently affect the performance of our group of patients in n-back tasks. There was, however, an interaction between dopaminergic state and domain, corresponding to a positive impact of levodopa on the spatial, but not letter or face, n-back tasks. This spatial domain effect can be explained by the fact that nigrostriatal dopaminergic deprivation is inhomogeneous within the striatum, affecting more severely the dorsal part of the caudate nucleus, where it reaches 90%, than the ventral caudate regions[28]. Studies in monkeys and in humans suggest that the dorsal caudate nuclei are more involved in visuospatial WM[29,30], possibly because they play a role in integration between spatial information and motor preparation. The area within the striatum which suffers the most severe dopamine depletion in PD is presumed to mostly subserve spatial cognition including spatial WM[9]. The impairment of spatial WM in early stages of PD could be supportive of this hypothesis, whereas WM for shapes and words, being dependent on more ventral regions of the caudate nuclei, may be affected in a more advanced stage of the disease[8,9]. The fact that our patients, displaying a deficit in different domains, were assessed at a later stage of the disease than those in the studies reporting an isolated spatial WM deficit[9] is in line with this theory. It can be hypothesized, thus, that our group of PD patients had supplementary brain lesions that could explain a more global WM deficit.

In conclusion, we have demonstrated the existence of a global impairment of WM in PD patients unrelated to motor dysfunction severity, executive function performance, mood, age, and education level. With the exception of improvement of spatial tasks, levodopa had no effect on WM. The spatial WM deficit may directly result from the nigrostriatal dopaminergic denervation that subsequently disrupts dorsolateral prefrontal-dorsal caudate nucleus pathways. As the disease progresses, other neural systems are more affected and may account for the

global, levodopa-refractory WM impairment observed in later stages of the disease. Our study also suggests that this WM deficit could be related to a short-term memory impairment, regardless of the nature of the information being processed or the level of processing.

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