PERGAMON

Neuropsychologia 41 (2003) 1442–1451

NEUROPSYCHOLOGIA

www.elsevier.com/locate/neuropsychologia

Dissociable effects of dopaminergic therapy on spatial versus non-spatial working memory in Parkinson's disease

H. Mollion[a], J. Ventre-Dominey[a,*], P.F. Dominey[a], E. Broussolle[b]

[a] CNRS-UMR 5015, 67 Boulevard Pinel, 69500 Bron, France
[b] Hôpital Neurologique Pierre Wertheimer, 59 Boulevard Pinel, 69003 Lyon, France

Received 3 October 2002; received in revised form 24 February 2003; accepted 30 April 2003

Abstract

There is now evidence for definite and early cognitive deficits in Parkinson's disease (PD), involving, in particular, executive functions and working memory. However, the distinction between visuo-spatial and non-spatial working memory deficits and the impact of dopamine on these deficits are still open to debate. The aim of this study was therefore to investigate cognitive and motor performance in PD patients in two conditional associative learning tasks requiring either spatial or non-spatial visual working memory. The subject had to point to visual targets according to the visual characteristics of memorised visual cues (colour, position and form). To assess the effect of L-dopa therapy, PD patients were studied over two consecutive days: one ON/OFF group of nine PD patients with treatment (ON condition) on the first day and without treatment (OFF condition) on the second day; and another OFF/ON group of nine PD patients tested on reverse. The PD groups were compared to a control group of nine age-matched healthy subjects. Our main data demonstrate that: (1) in PD patients with OFF treatment, the response time of manual pointing is increased mainly in the non-spatial working memory task; and (2) in PD patients with ON treatment, either the response time is normal (on the first day) or is increased in both visuo-spatial and non-spatial tasks. We suggest that this dissociation between spatial versus non-spatial working memory deficits in non-medicated PD might be related to compensatory mechanisms that occur following fronto-striatal dysfunction.

Keywords: Fronto-striatal dysfunction; Cognitive deficits; Conditional associative learning; L-Dopa therapy; Compensatory mechanisms

1. Introduction

According to the Alexander, Delong, and Strick (1986) model, topographically organised cortical projections converge on distinct regions of the striatum, which project through the basal ganglia output nuclei and thalamus back to distinct frontal areas, thus forming parallel circuits involved in both motor and non-motor cognitive processes. The nigro-striatal dopaminergic depletion in idiopathic Parkinson's disease (PD) results in a disruption of these different cortical–sub-cortical loops and consequently in clinical disorders including motor impairment, as characterised by the well-known triad of akinesia, rigidity and tremor, along with cognitive signs, occurring even early in the course of the disease (Cooper, Sagar, Jordn, Harvey, & Sullivan, 1991; Pillon et al., 1997; Taylor, Saint-Cyr, & Lang, 1990). The principal cognitive deficits described in PD concern "frontal" executive functions, including working memory and visuo-spatial abilities (Bradley, Welch, & Dick, 1989; Dalrymple-Alford, Kalders, Jones, & Watson, 1994; Hodgson, Dittrich, Henderson, & Kennard, 1999). However, depending on the tasks, the stage of the disease, and the L-dopa therapy status, these different studies report somewhat conflicting data related to cognitive visuo-spatial disturbances in PD. For example, in a conditional associative learning (CAL) paradigm using spatial and object modalities, Postle, Locascio, Corkin, and Growdon (1997) found in early medicated PD patients, a selective impairment in the CAL spatial condition and no deficit in the object condition. Likewise, Owen, Iddon, Hodges, Summers, and Robbins (1997) have studied three groups of PD patients in distinct working memory tasks to dissociate the different deficits according to the stage of the disease. The only observed deficit in mild medicated patients concerned visuo-spatial working memory, while verbal and visual non-spatial working memories were spared. On the contrary, no deficit was found in de novo and non-medicated patients while the most severe patients were impaired in all three working memory tasks. Based on these data, they suggested that the cognitive deficits progress with the course of the disease, with the most specific and early cognitive

---

* Corresponding author. Tel.: +33-4-37911212; fax: +33-4-37911210.
E-mail address: ventre@isc.cnrs.fr (J. Ventre-Dominey).

0028-3932/03/$ – see front matter © 2003 Elsevier Science Ltd. All rights reserved.
doi:10.1016/S0028-3932(03)00114-3

symptom of PD concerning visuo-spatial working memory. In contrast, Pillon et al. (1998) failed to find a specific deficit in medicated PD patients in a visuo-spatial working memory task compared to a verbal working memory task. For these authors, the visuo-spatial working memory deficit, as previously described, could result from a non-specific impairment in cognitive functions, particularly strategic and attentional processes, which are involved in visuo-spatial working memory tasks. Thus, whether or not visuo-spatial working memory is disrupted in medicated PD, and how L-dopa medication acts on this cognitive function remains an open issue.

In this study, we addressed these questions by comparing motor performance in PD patients in a behavioural task requiring either spatial or non-spatial visual working memory. We used a paradigm based on conditional associative learning in which the two working memory tasks differed only by the "position" or "form" of a memorised visual cue. Furthermore, to assess the effect of L-dopa on these processes, the same patients performed the cognitive tasks over two consecutive days either under anti-Parkinsonian treatment (ON condition) or after withdrawal (OFF condition).

2. Material and methods

2.1. Subjects

Motor performance was studied in two groups of nine patients with mild to moderate idiopathic Parkinson's disease compared to a group of nine age-matched healthy subjects. The patients were recruited from, and monitored in, the neurology clinic of the Wertheimer Neurology Hospital of Lyon. The diagnosis of PD was established according to the criteria of the UK Parkinson's Disease Brain Bank (Gibb & Lees, 1988) and the severity of illness was assessed with the Hoehn and Yahr (1967) scale. All the patients received L-dopa therapy and/or dopamine agonists which induced definite but moderate motor fluctuations at the time of the study. No patient received anticholinergic drugs. Motor performance of PD patients was evaluated over two consecutive days: (1) in one PD group (ON/OFF group: six males and three females), on the first day in ON condition (under anti-Parkinsonian treatment) and on the second day in OFF condition (after overnight withdrawal of all anti-Parkinsonian treatments); and (2) in one another matched PD group (OFF/ON group: six males and three females), on the first day in OFF condition and on the second day in ON condition.

For each ON and OFF condition, motor symptoms were assessed using the Unified Parkinson's Disease Rating Scale (UPDRS III) (Table 1). Like the PD groups, the control group (CT) underwent the tests over two consecutive days. No subject had history of psychiatric or neurological disease. All patients and control subjects gave their informed consent before inclusion in the study.

2.2. Neuropsychological tests

Cognitive status and frontal involvement were evaluated in the CT and PD groups, only in ON condition, using,

Table 1
Clinical characteristics of PD patients

Group	Patient no.	Age (years)	Duration of illness (years)	Hoehn and Yahr staging (ON)	UPDRS III ON (maximum score = 108)	UPDRS III OFF (maximum score = 108)	MMSE (maximum score = 30)
OFF/ON group	1	44	4	2	17	24	30
	2	48	5	1.5	15	22	28
	3	52	6	1.5	15	22	30
	4	54	3	2	10	14	30
	5	54	11	2	20	40	29
	6	59	16	2.5	15	26	29
	7	63	8	2	18	26	29
	8	68	5	2.5	14	22	29
	9	69	11	2	12	22	29
Mean ± S.D.		56.8 ± 8.6	7.7 ± 4.2	2 ± 0.4	15.1 ± 3	24.2 ± 6.9	29.2 ± 0.7
ON/OFF group	10	41	8	1.5	9	19	30
	11	41	11	2.5	16	24	29
	12	52	8	1.5	12	30	28
	13	54	8	2	16	27	29
	14	58	7	2	18	26	30
	15	68	4	2	13	18	29
	16	69	11	2	26	31	30
	17	70	11	2.5	27	31	30
	18	72	7	2.5	15	20	29
Mean ± S.D.		58.3 ± 12.2	8.3 ± 2.3	2 ± 0.4	16.9 ± 6	25.1 ± 5.1	29.3 ± 0.7
Total PD group		57.6 ± 10.3	8 ± 3.3	2 ± 0.4	16 ± 4.7	24.7 ± 4.7	29.3 ± 0.7

respectively, the Mini Mental State Examination (MMSE, maximum scoring = 30) (Folstein, Folstein, & McHugh, 1975) and the Wisconsin Card Sorting Test (WCST). The WCST administration was displayed to the subject by computer using the Neuroscan Cardsort Test (version 3.2, Neurosoft, USA).

2.3. Methods

2.3.1. Experimental set-up

The subject was seated in a dimly lit room in an armchair in front of an adjustable set-up with a computer screen, a semi-reflective mirror and a touch sensitive screen. Head movements were prevented by using a chin rest. The touch screen was supported above the subject's lap, thus providing an ergonomically comfortable pointing area. Visual stimuli were displayed on the computer and reflected by the mirror to form a virtual image on the touch screen. The subject was instructed to point as fast as possible on the touch screen to the virtual image of visual targets (white square) that appeared at 10° right and left of the centre. The manual pointing was performed in closed loop condition (i.e. with vision of the pointing hand). Eye position was monitored by EOG recordings of the horizontal and vertical eye movements. An interactive software (Cortex, NIH) displayed the visual stimuli and collected data related to manual pointing (response time (RT) and position).

2.3.2. Paradigm: conditional associative learning

The conditional associative learning task relies on the association between the colour of a central cue and the direction of the manual pointing. The manual pointing response corresponds to a movement of the hand from a "lever" displayed at the bottom of the screen (starting hand position) to one of the two eccentric visual targets (±10°). As shown in Fig. 1, the paradigm is divided into three different sessions: one simple CAL (SIM) session with a single coloured cue, and two ambiguous CAL sessions with two simultaneous coloured cues displayed at the centre of the screen.

2.3.2.1. Simple CAL. In each trial, as soon as the subject presses the lever (L), the two visual targets (T) appear, followed by the central coloured cue (red or blue). The subject has to learn the association between the cue colour (Fig. 1) and the movement direction by trial and error. If the response is correct (i.e. the subject touches the correct target), this target changes into the colour of the cue. If the response is incorrect, the screen is cleared. The association rule for the two learned colours (LC) during the SIM task remains identical over the successive sessions (red–left, blue–right).

2.3.2.2. Ambiguous CAL. In each trial, after the lever is pressed, a single white cue is first presented for 1 s, then the visual targets and two coloured cues are displayed. The one of these two coloured cues that matches the characteristic (position or shape) of the initial cue is then processed based on its colour. According to the initial cue characteristics, the ambiguous CAL is performed in two sessions as follows (Fig. 1):

(a) *Spatial CAL* (*SPA*): For each trial, the initial cue (white square) can be in two different positions of the screen along its vertical central axis ("up" or "down"). The subject should then recognise which of the two coloured cues occurs in the same position as the initial cue, and

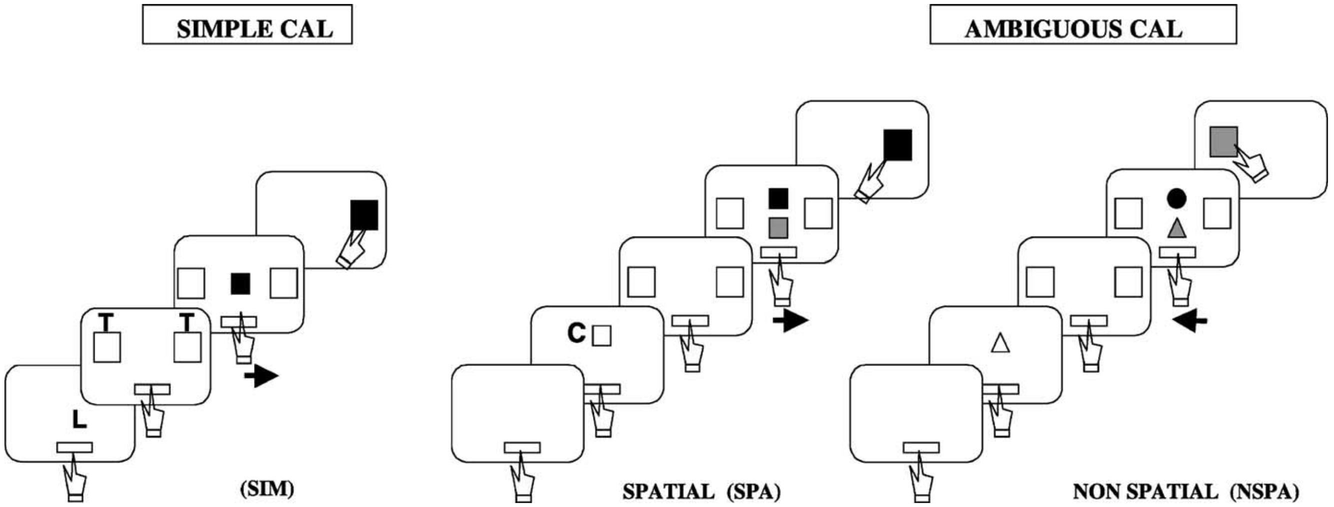

Fig. 1. Schema of the conditional associative learning (CAL) paradigm divided into a simple session and two ambiguous sessions. In the simple (SIM) session, one colour is displayed at a time at the centre of the screen and the subject has to associate the cue colour to a manual pointing direction: example of a trial with the blue cue (black area) associated to a movement direction to the right. The ambiguous CAL is divided into two sessions: a visuo-spatial one (SPA) with a supplementary uncoloured cue (C) displayed in different positions of the screen; and another one non-spatial (NSPA) with a supplementary uncoloured cue of different shapes displayed at the centre of the screen. After having memorised the supplementary cue characteristics, the subject has to associate either the cue colour and position (SPA) or the cue colour and shape (NSPA) to a manual pointing direction. T: visual target; L: lever of the starting hand position.

associate its colour with the movement to produce based on the learned rule.

(b) *Non-spatial CAL* (*NSPA*): The initial cue presented at the centre of the screen can have two different shapes (triangle or circle). The subject should then recognise which of the two coloured cues is of the same shape as the initial cue and use its colour to produce the movement based on the learned rule.

2.3.3. Time course of the paradigm

A first SIM session consists of several blocks of 16 trials each. The subject is told to find by trial and error the association between the cue colour and the direction of the pointing to the visual target (red–left, blue–right). This session terminates once the subject performs a complete block with at least 85% of correct trials. SIM sessions of eight trials each are then repeated after each ambiguous CAL session to monitor the level of motor performance and also the fatigue at the end of the test.

For the two ambiguous CAL sessions, a block of eight trials is first presented with the two previously learned colours to familiarise the subject with the session. Three blocks of 16 trials each are then displayed. These blocks are consisting of LC trials alternating with trials of two new colours (NC) for which the association is required to be learned by trial and error. In these sessions, the subject is told to memorise the position or the shape of the initial cue, then to find the colour that matches the characteristic of the cue and produce the movement associated to this colour according to the rule previously learnt with the LC (red–left, blue–right) or to the new rule to extract with the NC.

For each subject, as the whole test is performed twice over two consecutive days, different NC colours are used over the different sessions for the 2 days.

2.4. Data analysis

2.4.1. Neuropsychological test

Data analysis was performed on the MMSE test results for the number of correct responses and on the WSCT for the following variables: total number of responses, number of correct responses, number of categories achieved, percent of errors (total percent of errors, percent of perseverative errors and percent of non-perseverative errors), percent of perseverative responses, failure to maintain set and conceptual level response. Student's *t*-tests were performed on each variable of each test to compare the performance between the two PD groups and the CT group.

2.4.2. CAL paradigm

Analysis of the visuo-motor responses was performed for each trial and the following parameters of the motor responses were calculated:

- the percent of errors of manual pointing (or EP) corresponding to the ratio of the total number of errors to the effective trials number for one session;
- the response time, calculated as the time between the onset of the coloured cue on the screen and the effective pointing onto the target, for the correct responses only;
- an index of RT variation over the two consecutive days calculated by the following equation:

$$\Delta\mathrm{VAR} = \left[\frac{\mathrm{RTDay1} - \mathrm{RTDay2}}{\mathrm{RTDay1} + \mathrm{RTDay2}}\right] \times 100.$$

The statistical analysis was performed by a repeated measures ANOVA using the STATISTICA software package. The dependent variables were: EP, RT and ΔVAR of each session. The between-subject factor was the group (CT, ON/OFF and OFF/ON groups) and the within-subject factors were the different sessions (SIM, SPA and NSPA), and the day (days 1 and 2). As the SIM session was repeated three times during one daily test, we compared the motor performance between these different sessions each day for each group (CT, ON/OFF and OFF/ON groups) using a repeated measures ANOVA. Planned comparison were used to assess post-hoc comparisons. The significance level was determined at a confidence interval of 95%.

3. Results

3.1. Neuropsychological tests

For the MMSE test, no difference was found between the OFF/ON group (29.2 ± 0.7), the ON/OFF group (29.3 ± 0.7) and the CT group (29.2 ± 0.8).

In contrast, analysis of the WSCT showed significant deficits in the ON/OFF group ($P < 0.05$) and the OFF/ON group ($P < 0.05$) as compared to the CT group including: number of categories achieved, percent of errors (total percent of errors, percent of perseverative errors and percent of non-perseverative errors), percent of perseverative responses and conceptual level response (Table 2).

3.2. CAL paradigm

As no statistically significant difference was observed over the different SIM sessions ($P > 0.05$), we calculated a mean SIM value for RT and EP for each group and each day and used this mean value for further comparison.

To evaluate the effect of the task complexity, we analysed the motor performance in the CT group: no significant difference in motor performance was found between SPA and NSPA tasks (main task effect: $F(1, 8) = 0.9$, $P > 0.05$; task × day interaction: $F(1, 8) = 3.7$, $P > 0.05$).

3.2.1. Effect ON versus OFF treatment (between-groups comparison)

In the three CAL tasks, motor performance was impaired in the PD groups in both ON and OFF conditions as compared to the CT group (Table 3 and Fig. 2).

Table 2
Results of the Wisconsin Card Sorting Test

	CT group	PD patients		
		ON/OFF group	OFF/ON group	Total PD group
Total responses	104.3 ± 23.5	112.6 ± 14.8	113.3 ± 13.2	110 ± 13.6
Correct responses	76.6 ± 11.5	**66.2 ± 6.3**	**67.1 ± 8.2**	**66.7 ± 7.1**
Categories achieved	4.8 ± 1	**3 ± 2.1**	**3.4 ± 2.6**	**3.2 ± 2.2**
Total errors made (%)	24.8 ± 9.6	**39.2 ± 12.9**	**39.4 ± 12.3**	**39.3 ± 12.2**
Perseverative errors (%)	15.6 ± 6.9	**24.2 ± 7.7**	**22.1 ± 6.8**	**23.1 ± 7.1**
Non-perseverative errors (%)	9.2 ± 4.2	**15.6 ± 7.7**	**17.3 ± 8.2**	**16.4 ± 7.7**
Perseverative responses (%)	16.9 ± 7.6	**26 ± 8.4**	**24.1 ± 7**	**25 ± 7.6**
Failure to maintain set	2 ± 1.8	1.67 ± 1.22	2 ± 1.7	1.8 ± 1.4
Conceptual level response (%)	68.4 ± 13.8	**45.9 ± 21.9**	**47.7 ± 17.6**	**46.9 ± 19.3**

The values are given as mean ± S.D. Bold numbers indicate significant difference to the CT group at $P < 0.05$.

- *Day 1* (*naive condition*): On day 1, in the OFF/ON group, RT was significantly increased in all CAL tasks (planned comparison: $P < 0.01$) as compared to the CT group (main group effect: $F(2, 24) = 3.4$, $P < 0.05$; group × task interaction: $F(4, 48) = 0.4$, $P > 0.05$). Interestingly, a significant RT difference was found between the OFF/ON and ON/OFF groups only in the NSPA task (planned comparison: $P = 0.008$). In contrast, in the ON/OFF group, no significant RT defects were observed in either task (planned comparison as compared to CT group: $P > 0.05$). As shown in Fig. 3A, in the OFF/ON group, RT was significantly increased in both tasks as compared to the CT group and more specifically in the NSPA task as compared to the ON/OFF group. No significant differences in the percent of errors ER were found in either tasks between ON/OFF, OFF/ON and CT groups (main group effect: $F(2, 24) = 0.03$, $P > 0.05$; group × task interaction: $F(4, 48) = 0.4$, $P > 0.05$).
- *Day 2* (*after learning condition*): On day 2, though RT decreased in all groups (Fig. 3B), it remained slightly abnormal in PD groups (main group effect: $F(2, 24) = 3.2$, $P = 0.058$; group × task interaction: $F(4, 48) = 2$, $P = 0.1$). In the ON/OFF group, a significantly increased RT was found only in the NSPA task (planned comparison as compared to CT group: $P = 0.015$). Strikingly, more defects were observed in the OFF/ON group as RT remained abnormally increased in both SPA and NSPA tasks (planned comparison to CT group: $P < 0.001$). On day 2, the number of errors ER was normal in the two PD groups (main group effect: $F(2, 24) = 0.58$, $P > 0.05$; group × task interaction: $F(4, 48) = 0.8$, $P > 0.05$).

3.2.2. Effect ON versus OFF treatment over two consecutive days (within-groups comparison)

Interestingly, when we compared performance over the two consecutive days *within each group*, i.e. before and after learning the tasks, the effect of practice was highly dependent on the medication status over the 2 days and the task in the PD groups (main group effect: $F(2, 24) = 3.5$, $P < 0.05$; main day effect: $F(2, 24) = 20$, $P < 0.001$; group × task × day interaction: $F(4, 48) = 2.5$, $P = 0.055$). Explicitly, when we compared the day/medication effect on SPA and NSPA tasks performance only in the two PD groups, we found a significant group × task × day interaction ($F(1, 16) = 5.2$, $P = 0.036$).

In the CT group, as expected in repetitive task learning, an improvement of RT over the 2 days was observed in both SPA and NSPA tasks (planned comparison day 1/day 2:

Table 3
Table of the manual pointing RT and EP values (mean ± S.D.) in the three CAL tasks: simple (SIM), spatial (SPA) and non-spatial (NSPA) on the two consecutive days

	RT (ms)			EP (%)		
	SIM	SPA	NSPA	SIM	SPA	NSPA
CT group						
Day 1	1004 ± 79	1792 ± 304	1738 ± 243	2.9 ± 6.5	34.5 ± 17.5	18.5 ± 21.2
Day 2	1002 ± 128	1449 ± 260	1570 ± 178	4 ± 8.7	18.5 ± 17.2	9.8 ± 4.2
ON/OFF group						
Day 1-ON	1205 ± 137	2000 ± 499	1856 ± 471	3.5 ± 4.2	30.3 ± 20.2	20.8 ± 19.3
Day 2-OFF	1206 ± 183	1624 ± 298	1884 ± 661	2.2 ± 2.8	21.9 ± 18.4	21 ± 18.3
OFF/ON group						
Day 1-OFF	1360 ± 316	2206 ± 603	2227 ± 655	1.4 ± 2.2	33.2 ± 17.2	24.4 ± 19.3
Day 2-ON	1165 ± 179	2014 ± 597	1984 ± 534	3.2 ± 5	22.5 ± 22.5	21.1 ± 14.4

ON: under L-dopa therapy; OFF: after L-dopa release.

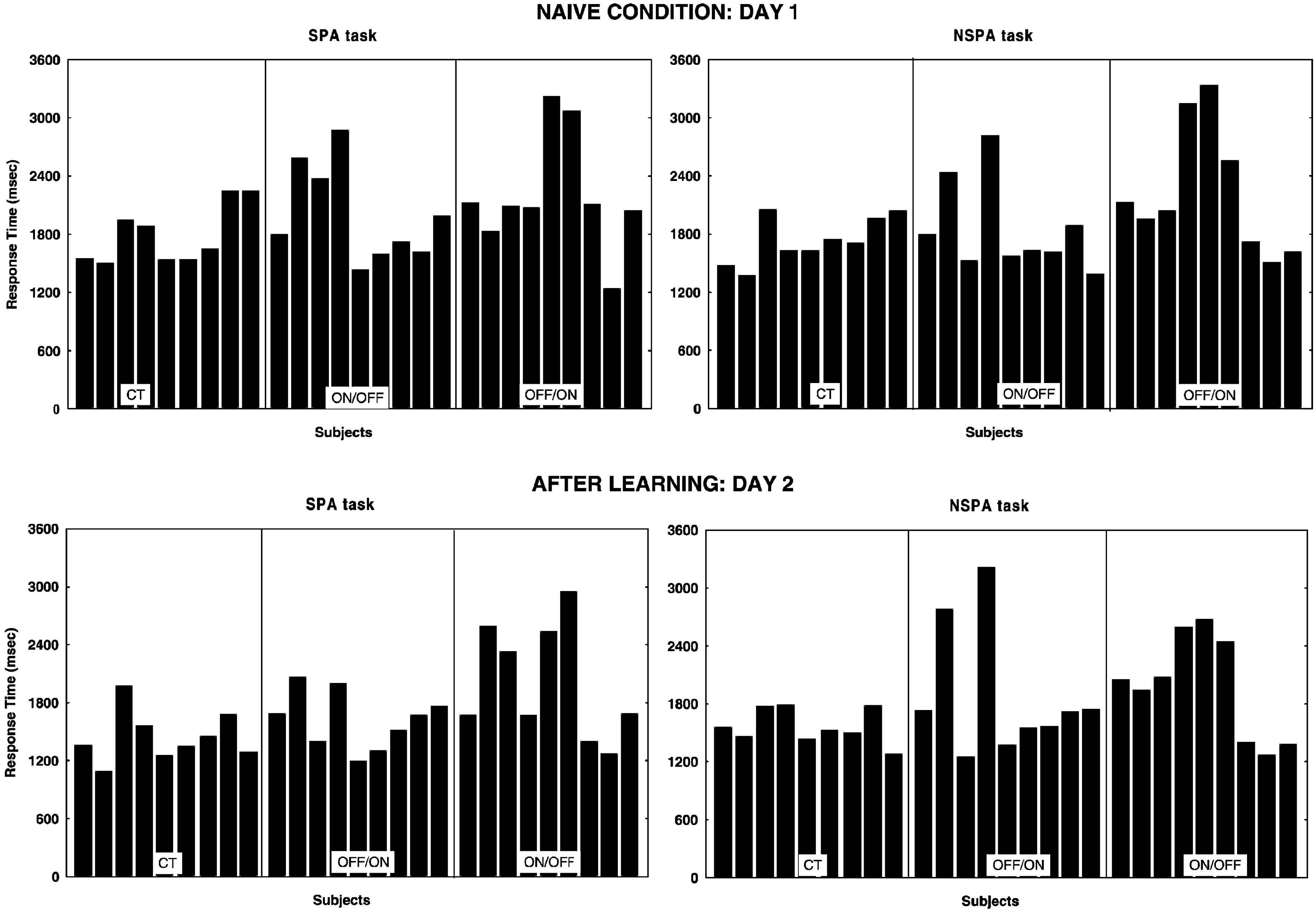

Fig. 2. Graph of the individual values of response time (RT) in the three groups (CT, ON/OFF and OFF/ON) on day 1 (naive condition) and day 2 (after learning condition) in the two ambiguous CAL tasks, spatial (SPA) and non-spatial (NSPA).

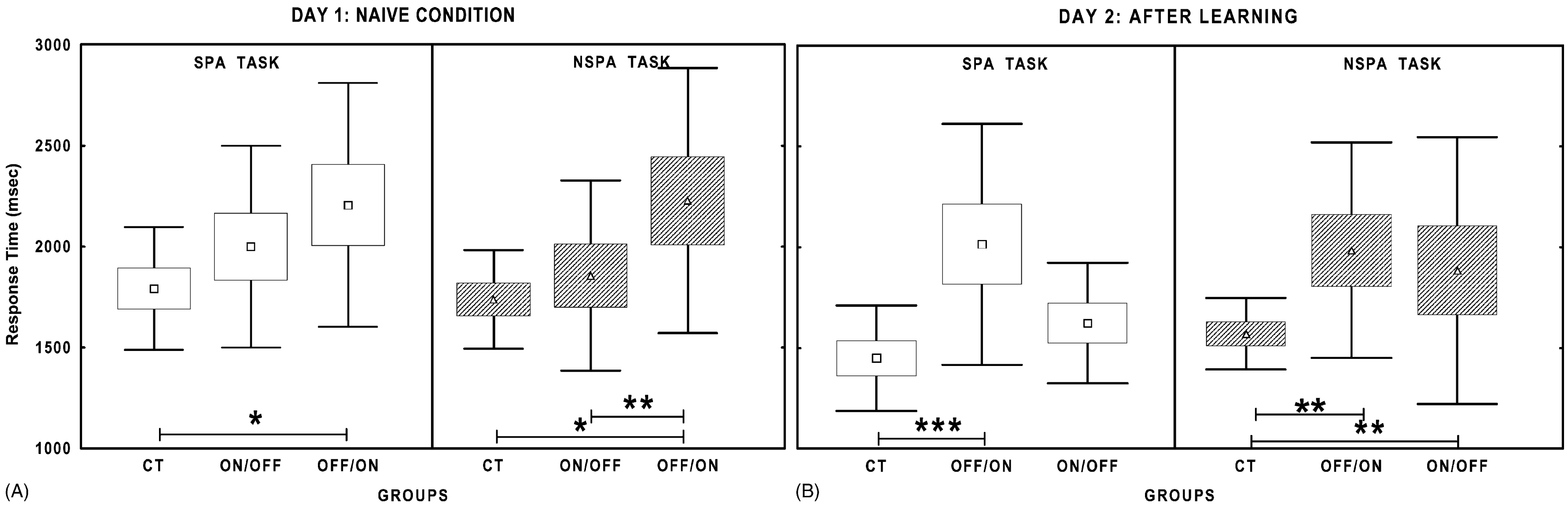

Fig. 3. Graph of the mean RT in the three groups (CT, ON/OFF and OFF/ON) in the spatial (SPA) and non-spatial (NSPA) tasks, on two consecutive days: (A) day 1, naive condition; (B) day 2, after learning condition. Standard deviations are presented: $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

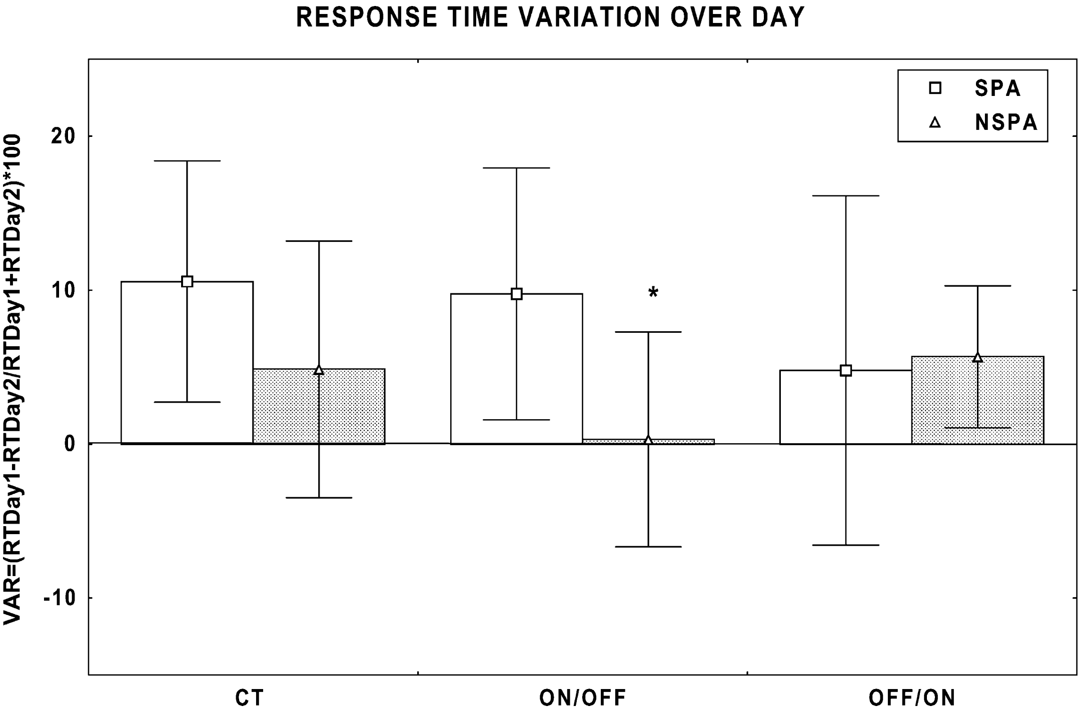

Fig. 4. Graph of the RT variation over days (ΔVAR) in spatial (SPA) and non-spatial (NSPA) tasks and in the three groups (CT, ON/OFF and OFF/ON). Standard deviations are presented: $^*P < 0.05$.

$P < 0.05$). In the ON/OFF group, RT improved on the second day, even OFF treatment, only in the SPA task (planned comparison day 1-ON/day 2-OFF: $P < 0.001$). In contrast, in the NSPA task, RT on day 2 was either unchanged or slightly increased after learning (planned comparison day 1-ON/day 2-OFF: $P > 0.05$). Furthermore, in the ON/OFF group, RT was significantly increased in the NSPA task as compared to the SPA task (planned comparison: $P < 0.05$). In contrast, the OFF/ON group like the CT group benefits from practice as RT significantly decreased in both NSPA and SPA tasks on the second day ON condition (planned comparison: $P < 0.05$).

To confirm the day 1/day 2 learning effect on motor performance in each group, we calculated for each SPA and NSPA task the following index $\Delta\text{VAR} = [(\text{RTDay1} - \text{RTDay2})/(\text{RTDay1} + \text{RTDay2})] \times 100$. The higher the index ΔVAR, the more RT decreases on the second day. Only in the ON/OFF group, a significant difference of ΔVAR was found (main task effect: $F(2, 48) = 5.8$, $P < 0.01$; group × task interaction: $F(4, 48) = 2.8$, $P < 0.05$) between the two NSPA and SPA tasks (planned comparison: $P < 0.05$). As shown in Fig. 4, the ΔVAR shows an RT improvement after learning in the SPA task in all the CT and PD groups, even OFF treatment, and no improvement in the NSPA task only in the ON/OFF group. This index measurement makes clear a significant lack of cognitivo-motor performance in the NSPA task, for the PD group after DOPA withdrawal.

4. Discussion

The aim of this study was to explore cognitive and motor performance of PD patients in a working memory task requiring cognitive visual information processing. Using a conditional associative learning paradigm, we compared visuo-spatial versus non-spatial, working memory abilities in ON and OFF L-dopa medication conditions over two consecutive days. The main finding of this study correspond to a significant deficit in manual pointing occurring as an abnormal response time in OFF condition, specifically in the non-spatial working memory task. Indeed, while the control subjects always improved their performance after learning in both spatial and non-spatial tasks, the ON/OFF PD patients, improved their performance after learning (tested on the second day) only in the SPA task and not in the NSPA task. Such a specific deficit cannot be attributed to an impairment in motor execution due to PD, as the motor execution is similarly elicited in all the tasks, either SIM, SPA and NSPA. Thus, a response time deficit due to a disruption in motor execution should have been observed in all three task modalities. A fatigue side effect can also be excluded as the response time of the manual pointing remains unchanged between the initial and the last SIM task presented at the end of the paradigm. Thus, it is likely that the deficit observed in our PD patients results more from a cognitive (including working memory) dysfunction, than from a motor execution dysfunction. Accordingly, based on neuropsychological results from the WSCT, our PD patients demonstrated disorders in cognitive executive functions disclosed by a perseverative behaviour and difficulties in elaboration and maintenance of a behavioural set. Furthermore, our paradigm requires different cognitive resources, including working memory and attention. Thus, in the simple CAL session of our paradigm, the subject has to learn a rule that is the arbitrary association between a colour and a movement direction. In the ambiguous CAL session, in addition to the learned associative rule, the subject has to take into account and memorise the characteristics (position or shape) of a supplementary cue in order to perform the task. Thus, the ambiguous CAL tasks require additional cognitive resources, including attention and working memory. Previous studies have shown impairment in PD patients particularly when the tasks are complex and require a higher level of processing (for example, performing two simultaneous motor or cognitive tasks) (Brown & Marsden, 1990, 1991; Dalrymple-Alford et al., 1994; Malapani, Pillon, Dubois, & Agid, 1994). In this condition of task complexity, PD patients displayed difficulties in simultaneously processing different or contradictory information, especially in OFF treatment condition (Malapani et al., 1994). These difficulties could be linked to a quantitative deficit of cognitive resources or to a defect in their allocation (Brown & Marsden, 1991). Likewise, in our study, one can ask whether or not the defects observed in PD patients might be due to an excessive attentional load related to the paradigm. In the ambiguous CAL, the attentional demands are equivalent in the SPA and the NSPA conditions. In consequence, if the deficits observed in our PD patients in OFF condition were strictly related to such an attentional cognitive demands, they should have been equally distributed in the SPA and in the NSPA conditions, contrary to our observation. As the SPA and the NSPA sessions differ only by the modality of the supplementary cue, that is, position or shape, the specific defects in NSPA condition is likely reflecting a disruption in the object recognition working memory process disclosed after medication withdrawal. Therefore, we suggest that the deficits in response time and the (less significant) increase of errors found in our non-medicated PD patients reflects a deficit of the working memory related to the integration of non-spatial visual information.

Visual working memory relies onto two sub-systems, one related to spatial localisation and the other related to object recognition. As shown in the monkey by electrophysiological single unit recording studies (Wilson, Scalaidhe, & Goldman-Rakic, 1993) and in human by neuroimaging studies (Courtney, Ungerleider, Keil, & Haxby, 1996), these two sub-systems likely rely on distinct prefrontal neuronal populations: (1) one in the inferior convexity, receives inputs from the occipito-temporal pathway (the “what” ventral stream) and is involved in the non-spatial working memory (faces and objects); and (2) the other, in the dorsolateral convexity, is connected to the posterior parietal cortex (the “where” dorsal stream) and is dedicated to spatial processing (localisation and topography). However, the topic remains open as this functional and anatomical dissociation in working memory processing has not been reported in other imagery studies in human (Postle, Stern, Rosen, & Corkinb, 2000). In Parkinson’s disease, due to the striato-prefrontal loop dysfunction, impairments in working memory tasks are often described (Cooper et al., 1991; Taylor et al., 1990). However, contrasting with our data, a predominant deficit in visuo-spatial working memory has been reported in some studies comparing visuo-spatial versus visual non-spatial working memory abilities in PD (Bradley et al., 1989; Owen et al., 1997; Pillon et al., 1997; Postle et al., 1997). For some authors, this visuo-spatial deficit could specifically occur very early in the course of the disease (Owen et al., 1997; Pillon et al., 1997). For others, the deficits observed in PD are linked more to the intrinsic difficulty of the tasks, that require additional processing than to a specific lack in visuo-spatial working memory (Brown & Marsden, 1990; Pillon et al., 1998). Indeed, the results reported in these different studies are highly dependent on the nature of the tasks used and the stage of the disease. In contrast to our current study, previous studies often investigate PD patients under dopaminergic medication and the effect of the treatment release is rarely evaluated. Like Pillon et al. (1998), we could not find specific deficits either in space nor in object recognition processes when PD patients were tested on the first day, ON medication. In contrast, when PD patients were tested on the first day, OFF medication, visual working memory was defective as compared to control subjects and to medicated PD patients, specifically in the processing of non-spatial form. Interestingly, after having learnt the tasks in the non-medicated condition, these PD patients remained abnormal, even with medication on the second day, in both spatial and non-spatial working memory tasks. Thus, even though these PD patients improved their performance from a day to another, they did not appear to benefit from the previous day of practice as did the controls or medicated PD patients. Such defects might be interpreted as a deleterious effect of dopaminergic removal on the memory of strategic processes that could be encoded in modified corticostriatal synapses. Indeed, it has been demonstrated that corticostriatal synaptic plasticity is severely impaired after chronic dopaminergic denervation (Centonze, Picconi, Gubellini, Bernardi, & Calabresi, 2001). Accordingly, deficits in procedural learning have been reported in PD patients (Krebs, Hogan, Hening, Adamovich, & Poizner, 2001; Sarrazin et al., 2002; Sommer, Grafman, Clark, & Hallet, 1999). However, further studies specifically devoted to learning and executive function, ON versus OFF medication, would be useful to provide better insights on dopaminergic influence on learning processes in PD. In contrast, in the same mild PD patients but only after medication removal, we demonstrated a significant disruption in working memory related to the ventral visual sub-system.

Interestingly, by neuroimaging studies, it has been demonstrated that medication removal in PD can induce hyperactivation in cortical areas of the dorsal visual stream, reflecting recruitment of compensatory mechanisms during sequential motor execution (Catalan, Ishii, Honda, Samii,

& Hallett, 1999; Rascol et al., 1997; Samuel et al., 1997) or motor imagery tasks (Thobois et al., 2000). This overactivation was described in different nervous structures, including the cerebellum and several cortical areas that include the primary motor cortex, the premotor lateral cortex and the parietal associative cortex and could be reversed by reintroduction of dopaminergic treatment (Jenkins et al., 1992; Rascol et al., 1994, 1997). Based on these results and our current data, we hypothesise that the dissociation in working memory deficits observed in PD patients after medication withdrawal could be linked to a specific recruitment of the dorsal circuits, thus compensating for the visuo-spatial working memory deficits. These different observations can partly explain some of the controversy of the literature related to working memory in PD and thus emphasise the influence of the type and level of the anti-Parkinsonian medication that can mask some of PD disorders.

Acknowledgements

This study has been founded by “la Fédération Française des Groupements de Parkinsoniens”.

References

Alexander, G. E., Delong, M. R., & Strick, P. L. (1986). Parallel organisation of functionally segregated circuits linking basal ganglia and cortex. *Annual Review of Neurosciences*, *9*, 357–381.

Bradley, V. A., Welch, J. A., & Dick, D. J. (1989). Visuospatial working memory in Parkinson’s disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *52*, 1228–1265.

Brown, R. G., & Marsden, C. D. (1990). Cognitive function in Parkinson’s disease: From description to theory. *Trends in Neurosciences*, *13*, 21–29.

Brown, R. G., & Marsden, C. D. (1991). Dual task performance and processing resources in normal subjects and patients with Parkinson’s disease. *Brain*, *114*, 215–231.

Catalan, M. J., Ishii, K., Honda, M., Samii, A., & Hallett, M. (1999). A PET study of sequential finger movements of varying length in patients with Parkinson’s disease. *Brain*, *122*, 483–495.

Centonze, D., Picconi, B., Gubellini, P., Bernardi, G., & Calabresi, P. (2001). Dopaminergic control of synaptic plasticity in the dorsal striatum. *The European Journal of Neuroscience*, *13*(6), 1071–1077.

Cooper, J. A., Sagar, H. J., Jordn, N., Harvey, N. S., & Sullivan, V. (1991). Cognitive impairment in early untreated Parkinson’s disease and its relationship to motor disability. *Brain*, *114*, 2095–2122.

Courtney, S. M., Ungerleider, L. G., Keil, K., & Haxby, J. V. (1996). Object and spatial visual working memory activate separate neural systems in human cortex. *Cerebral Cortex*, *6*, 39–49.

Dalrymple-Alford, J. C., Kalders, A. S., Jones, R. D., & Watson, R. W. (1994). A central executive deficit in patients with Parkinson’s disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *57*, 360–367.

Folstein, M. F., Folstein, S. E., & McHugh, R. R. (1975). A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, *12*, 189–198.

Gibb, W. R. G., & Lees, A. J. (1988). The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson’s disease. *Journal of Neurology, Neurosurgery and Psychiatry*, *51*, 745–752.

Hodgson, T. L., Dittrich, W. H., Henderson, L., & Kennard, C. (1999). Eye movements and spatial working memory in Parkinson’s disease. *Neuropsychologia*, *37*, 927–938.

Hoehn, M., & Yahr, M. (1967). Parkinsonism: Onset progression and mortality. *Neurology*, *17*, 427–442.

Jenkins, I. H., Fernandez, W., Playford, E. D., Lees, A. J., Frackowiak, R. S., & Passingham, R. E. (1992). Impaired activation of the supplementary motor area in Parkinson’s disease is reversed when akinesia is treated with apomorphine. *Annals of Neurology*, *32*, 749–757.

Krebs, H. I., Hogan, N., Hening, W., Adamovich, S. V., & Poizner, H. (2001). Procedural motor learning in Parkinson’s disease. *Experimental Brain Research*, *141*(4), 425–437.

Malapani, C., Pillon, B., Dubois, B., & Agid, Y. (1994). Impaired simultaneous cognitive task performance in Parkinson’s disease: A dopamine-related dysfunction. *Neurology*, *44*, 319–326.

Owen, A. M., Iddon, J. L., Hodges, J. R., Summers, B. A., & Robbins, T. W. (1997). Spatial and non-spatial working memory at different stages of Parkinson’s disease. *Neuropsychologia*, *35*, 519–532.

Pillon, B., Deweer, B., Vidhailet, M., Bonnet, A. M., Hahn-Barma, V., & Dubois, B. (1998). Is impaired memory for spatial location in Parkinson’s disease domain specific or dependant on ‘strategic’ processes? *Neuropsychologia*, *36*, 1–9.

Pillon, B., Ertle, S., Deweer, B., Bonnet, A. M., Vdailhet, M., & Dubois, B. (1997). Memory for spatial location in “de novo” Parkinsonian patients. *Neuropsychologia*, *35*, 221–228.

Postle, B. R., Locascio, J. J., Corkin, S., & Growdon, J. H. (1997). The time course of spatial and object learning in Parkinson’s disease. *Neuropsychologia*, *35*, 1413–1422.

Postle, B. R., Stern, C. E., Rosen, B. R., & Corkinb, S. (2000). An fMRI investigation of cortical contributions to spatial and nonspatial visual working memory. *NeuroImage*, *11*, 409–423.

Rascol, O., Sabatini, U., Chollet, F., Senard, J. M., Montastruc, J. L., Celsis, P., Marc-Vergne, J. P., & Rascol, A. (1994). Normal activation of the supplementary motor area in patients with Parkinson’s disease undergoing long-term treatment with levodopa. *Journal of Neurology, Neurosurgery and Psychiatry*, *57*, 567–571.

Rascol, O., Sabatini, U., Fabre, N., Brefel, C., Loubinoux, I., Celsis, P., Senard, J. M., Montastruc, J. L., & Chollet, F. (1997). The ipsilateral cerebellar hemisphere is overactive during hand movements in akinetic Parkinsonian patients. *Brain*, *120*, 103–110.

Samuel, M., Ceballos-Baumann, A. O., Blin, J., Uema, H., Boecker, H., Passingham, R. E., & Brooks, D. J. (1997). Evidence for lateral premotor and parietal overactivity in Parkinson’s disease during sequential and bimanual movements: A PET study. *Brain*, *120*, 963–976.

Sarrazin, M., Deweer, B., Merckl, A., Von Poser, N., Pillon, B., & Dubois, B. (2002). Procedural learning and striatofrontal dysfunction in Parkinson’s disease. *Movement Disorders*, *17*(2), 265–273.

Sommer, M., Grafman, J., Clark, K., & Hallett, M. (1999). Learning in Parkinson’s disease: Eyeblink conditioning, declarative learning, and procedural learning. *Journal of Neurology, Neurosurgery and Psychiatry*, *67*(1), 27–34.

Taylor, A. E., Saint-Cyr, J. A., & Lang, E. (1990). Memory and learning in early Parkinson’s disease: Evidence for a “frontal lobe syndrome”. *Brain and Cognition*, *13*, 211–232.

Thobois, S., Dominey, P. F., Decety, J., Pollak, P., Gregoire, M. C., Le Bars, D., & Broussolle, E. (2000). Motor imagery in normal subjects and in asymmetrical Parkinson’s disease: A PET study. *Neurology*, *55*, 996–1002.

Wilson, F. A. W., Scalaidhe, S. P. O., & Goldman-Rakic, P. S. (1993). Dissociation of object and spatial processing domains in primate prefrontal cortex. *Science*, *260*, 1955–1958.