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Hallucinations in Parkinson's disease
Prevalence, phenomenology and risk factors

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Summary
Hallucinations, mainly of a visual nature, are considered to affect about one-quarter of patients with Parkinson's disease. They are commonly viewed as a side-effect of antiparkinsonian treatment, but other factors may be involved. The aim of this study was to determine the phenomenology, prevalence and risk factors of hallucinations in Parkinson's disease. Two-hundred and sixteen consecutive patients fulfilling clinical criteria for Parkinson's disease were studied. Demographic and clinical variables were recorded, including motor and cognitive status, depressive symptoms and sleep–wake disturbances. Patients with and without hallucinations were compared using non-parametric tests, and logistic regression was applied to significant data. Hallucinations had been present during the previous 3 months in 39.8% of the patients, and fell into three categories: minor forms, consisting of a sensation of a presence (person), a sideways passage (commonly of an animal) or illusions were present in 25.5% of the patients (an isolated occurrence in 14.3%), formed visual hallucinations were present in 22.2% (isolated in 9.3%) and auditory hallucinations were present in 9.7% (isolated in 2.3%). Patients with minor hallucinations had a higher depression score than non-hallucinators but did not differ in other respects. Logistic regression analysis identified three factors independently predictive of formed visual hallucinations: severe cognitive disorders, daytime somnolence and a long duration of Parkinson's disease. These findings indicate that, when minor hallucinations are included, the total prevalence is much higher than previously reported. A simple side-effect of dopaminergic treatment is not sufficient to explain the occurrence of all visual hallucinations. The main risk factor in treated patients is cognitive impairment, although sleep–wake cycle disturbances, and possibly other factors related to the duration of the disease, act as cofactors.

Keywords: hallucination; Parkinson's disease; dementia; sleep–wake disorder

Abbreviations: CES-D = Center for Epidemiologic Studies depression score; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders; MMP = Mini-Mental Parkinson; UPDRS = Unified Parkinson's Disease Rating Scale

Introduction
Although mental disturbances in the course of Parkinson's disease, including delirium and hallucinations, were mentioned by early authors, they were thought to be rare and were considered by most clinicians to be either part of the ultimate progression of the disease or coincidental (Souques, 1921). After an epidemic of lethargic encephalitis, the picture was blurred by the coexistence of Parkinson's disease and postencephalitic cases, such as hallucinations and psychotic disorders, which were commonly observed in the course of postencephalitic syndromes (de Ajuriaguerra, 1971). In the years following the introduction of dopaminergic therapy, confused states and hallucinations were reported as a side-effect of levodopa and, later, of dopaminergic agonist therapy (Factor *et al.*, 1995).

Recently, the hallucinations of Parkinson's disease have again attracted attention. First, several prospective studies showed that hallucinations, mainly visual, affected as many as one-quarter of outpatients with Parkinson's disease (Sanchez-Ramos *et al.*, 1996; Graham *et al.*, 1997; Inzelberg *et al.*, 1998; Pappert *et al.*, 1999). Secondly, some investigators stated that hallucinations were a risk factor for permanent nursing home placement, with its associated high mortality rate (Goetz and Stebbins, 1993, 1995). Thirdly, the management of hallucinations requiring antipsychotic treatment has been improved by the development of new agents, such as clozapine, which may be used in Parkinson's disease patients with a low risk of aggravating motor symptoms (Cummings, 1999).

Several questions regarding hallucinations in Parkinson's disease remain controversial or unanswered. Minor forms of

hallucination, such as the sensation of a presence, have been reported but have not been studied systematically. The pathophysiology of the hallucinations is also poorly understood. Although hallucinations are commonly considered to be a side-effect of dopaminergic treatment, various mechanisms have been implicated (Factor *et al*., 1995; Mendis *et al*., 1996; Manford and Andermann, 1998) and other factors may intervene. Previous clinical studies have shown that the presence of cognitive impairment is associated with a higher risk of developing hallucinations (Meco *et al*., 1990; Sanchez-Ramos *et al.*, 1996; Graham *et al.*, 1997). However, the role of other factors, such as motor status, sleep disorders and depression, is controversial. The aims of this study were to establish, in a large population of outpatients with Parkinson's disease, the prevalence and characteristics of hallucinations, including minor forms, and to identify independent predictive factors for hallucinations among a set of clinical variables by the use of multivariate analysis.

Methods

Recorded data

Motor function was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) activities of daily living (UPDRS II) and motor (UPDRS III) subscales, and modified Hoehn and Yahr staging (Fahn *et al.*, 1987). Because axial symptoms may depend on non-dopaminergic lesions and have been found previously to correlate with cognitive impairment (Pillon *et al.*, 1989), we also calculated an 'axial score', defined as the sum of the following UPDRS III items: speech; rising from a chair; posture; postural stability; and gait (maximum score 20). In patients with fluctuating symptoms, the UPDRS II items were rated according to the best performance in the day, and the motor scores were determined while in the 'on' state. Patients were considered as fluctuating if they had akinetic fluctuations other than early-morning akinesia or corrected end-of-dose deterioration. They were considered as dyskinetic if they had dyskinesias scoring $\geqslant 2$ on Obeso's scale (Langston *et al.*, 1992).

Patients were defined as having severe sleep disorders if they had two or more of the following: difficulty falling asleep; more than one awakening during sleep; early morning awakening; nocturnal agitation; and vivid dreams. Daytime somnolence (not including a short rest period after lunch) was recorded according to statements of the patients and/or caregivers. The patients were asked if they had a known ocular pathology (including cataracts, retinal disease and glaucoma).

Global cognitive function was assessed using the Mini-Mental Parkinson (MMP), a recently developed and validated bedside cognitive test that is adapted to Parkinson's disease cognitive disorders (Mahieux *et al.*, 1995; Mahieux and Fénelon, 1998). In brief, the MMP consists of seven subtests (orientation, visual memory registration, visual memory recall, calculation, crossed verbal fluency, set-shifting and similarities). The maximum total score is 32. According to the validation studies, we classified cognitive status in three groups: normal (score between 32 and 29); moderately impaired (between 28 and 24); and severely impaired (below 24). Dementia was diagnosed by using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria A and B (American Psychiatric Association, 1994). The use of DSM criteria for the diagnosis of dementia in Parkinson's disease may raise some difficulties (see discussion in Mahieux *et al.*, 1998), and in some cases the diagnosis of dementia may be questionable. For the purpose of statistical analysis, we pooled the data for patients with certain dementia and suspected dementia. Mood was assessed using the French version of the Center for Epidemiologic Studies depression self-rating scale (CES-D) (Fuhrer and Rouillon, 1989).

Antiparkinsonian treatments were recorded, and the total daily dose of levodopa was calculated for each patient. In order to take into account the amount of all dopaminergic agents taken (i.e. levodopa and dopaminergic agonists), we calculated a levodopa-equivalent dose, using correspondences published previously or the available data comparing levodopa and dopaminergic agonists (Vidailhet *et al.*, 1990; Krack *et al.*, 1998), as follows: 10 mg bromocriptine = 1 mg lisuride = 4 mg ropinirole = 100 mg levodopa (with a dopa-decarboxylase inhibitor). As no equivalency data were available for piribedil, a dopaminergic agonist available in France, we considered 100 mg piribedil equivalent to 100 mg levodopa on the basis of primate studies (L. A. Smith, personal communication) and the clinical experience of French Parkinson's disease specialists.

On the basis of previous studies and our own clinical experience, we routinely questioned the patients on the presence of three types of hallucinatory phenomena during the previous 3 months: minor hallucinations/illusions; visual hallucinations; and auditory hallucinations. Minor hallucinations/illusions were defined as 'presence' hallucinations, 'passage' hallucinations and illusions (see description below). Earlier episodes of hallucinations were also recorded. The characteristics of the recent ($\leqslant$3 months) hallucinations were recorded using a semistructured questionnaire.

Patients

The patients were recruited consecutively in two Parkinson's disease clinics located in Paris (Hôpital Tenon and Hôpital Léopold Bellan). The outpatients were included in the study if they met the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for 'definite' Parkinson's disease (Hughes *et al.*, 1992), spoke fluent French and gave their informed consent. Two-hundred and sixteen patients were studied (141 from Tenon and 75 from Bellan). Their main characteristics are presented in Table 1. Only seven patients received no antiparkinsonian treatment, and another five received selegiline and/or anticholinergics with no dopaminergic treatment. One patient had received a unilateral

Table 1 *Characteristics of the patients (*n = *216)*

	Mean ± SD or %
Age (years)	69 ± 9.7
Age at onset of Parkinson's disease (years)	59.5 ± 10.9
Duration (years)	9.5 ± 6.2
Males (%)	56.9
Hoehn and Yahr stage in 'on' state	2.0 ± 0.8
UPDRS ADL score	10.6 ± 5.9
UPDRS motor score in 'on' state	15.4 ± 8.8
Axial score	3.7 ± 3.1
Presence of akinetic fluctuations (%)	38.9
Presence of dyskinesias (%)	31.9
CES-D (depression) score	19.2 ± 9.4
MMP (cognitive) score	25.2 ± 5.9
Presence of dementia (DSM) (%)	20.4
Treatment with levodopa (%)	90.7
Treatment with dopaminergic agonists (%)	47.2
Treatment with anticholinergics (%)	7.4
Treatment with amantadine (%)	11.6
Treatment with selegiline (%)	16.7
Levodopa daily dose (mg, n =196)	643 ± 383
Levodopa-equivalent daily dose (mg) (n = 204)	705 ± 414

ADL = activities of daily living.

intrastriatal graft of foetal mesencephalic cells and another patient had received bilateral pallidal stimulation. None of the patients had previously received a diagnosis of schizophrenia. One patient had a delusional disorder (persecutory type) known before the onset of Parkinson's disease.

Comparison of the patients recruited in the two centres revealed few differences. Compared with the patients seen at Bellan, those seen at Tenon Hospital had a lower UPDRS II score (mean 9.2 versus 13.4, $P > 0.001$), were less likely to have akinetic fluctuations (31 versus 53%, $P = 0.002$), received a lower daily dose of levodopa (mean 578 versus 759 mg, $P = 0.001$) and were less likely to receive amantadine (7.8 versus 18.7%). All the other variables, as well as the prevalence of hallucinations, were not significantly different.

Data analysis

The statistical analysis was performed using non-parametric tests. The results are presented as mean ± standard deviation in order to facilitate comprehension of the tables. We used the Mann–Whitney two-tailed *U*-test for comparison of two subgroups of patients for continuous variables, the Kruskal–Wallis test for global comparison of three subgroups of patients for continuous variables, and the χ^2 test for categorical variables. The multivariate analysis was performed using a stepwise logistic regression, submitting all covariates that showed statistical significance ($P < 0.05$). Continuous variables were dichotomized using the median as the cut-off value. Cognitive disorders were classified into two subgroups according to the MMP score: severe (MMP $<$ 24) and moderate or absent (MMP $\geqslant$ 24). Statistical analyses were performed with SPSS software (version 7.5) (SPSS Inc, Chicago, Ill., USA).

Table 2 *Prevalence of hallucinations in the study population (*n = *216) during the 3 months preceding inclusion*

Hallucination type	Total prevalence % (95% CI)	Prevalence when present in isolation % (95% CI)
Minor	25.5 (19.7–31.3)	14.3 (9.6–19.0)
Visual elaborate	22.2 (16.7–27.7)	9.3 (5.4–13.2)
Auditory	9.7 (5.8–13.6)	2.3 (0.3–4.3)
All types	39.8 (33.3–46.3)	

In some patients, two or three types of hallucinations occurred in combination. CI = confidence interval.

Results

Prevalence of hallucinations

Eighty-six patients (39.8% of the patients studied, 95% confidence interval = 33.3–46.3) had experienced hallucinatory phenomena within the 3 months preceding inclusion in the study. The frequencies of the different forms of hallucinations are shown in Table 2. In only two cases (2% of the patients with hallucinations) had the hallucinations occurred during the course of delirium (according to DSM-IV criteria), presumably related to antiparkinsonian treatment. Remote transient episodes of hallucinations (occurring >3 months before inclusion), commonly during an acute psychotic episode, had occurred in 35 patients (16.2%), 14 of whom had no hallucinations in the 3-month period preceding inclusion. Therefore, the total lifetime prevalence of hallucinations of all types was 46.3% (95% confidence interval = 39.7–52.9).

Phenomenology of the hallucinations

Minor hallucinations/illusions

We grouped together in this category (n = 55) three types of phenomena. The most frequent type was presence hallucinations (n = 35, 64%). The patient had the vivid sensation of the presence of somebody either somewhere in the room or, less often, behind him or her. In all cases, the presence was that of a person, and in one case it was also occasionally the presence of an animal (a rat). In seven cases, the presence was that of a relative (deceased in three cases). In all the other cases the presence was unidentified. The presence hallucinations were commonly as vivid as a hallucinated scene and were described as a 'perception'. For instance, one patient said: 'the image is behind me', a second said: 'I see someone arriving; I turn back but nobody is there', a third said: 'I take a look; I don't see anything, but it is engraved in my mind', and another said: 'I have the impression that my mother is always there, that she is about to come into sight'. The passage hallucinations (n = 18, 33%) consisted of brief visions of a person (six patients) or an animal (12

Table 3 *Repercussions of hallucinations*

	Isolated minor hallucinations (n = 31) (%)	Visual hallucinations (n = 48) (%)
Reported spontaneously	3.2	12.5
Coexisting anxiety	3.2	27.6
Coexisting delusions	0	8.5
Insight	96.8	77.0
Need for a therapeutic change	0	10.6

Table 4 *Content of formed visual hallucinations* (n = *48)*

	n (%)
Persons	35 (73)
Familiar	24 (50)
Deceased relatives	9 (19)
Unfamiliar	28 (58)
Animals	16 (33)
Others (objects)	9 (19)

patients) passing sideways. If an animal was seen, the species was almost invariably specified (commonly a cat or a dog), and in two instances it was a dog previously owned by the patient. Illusions occurred in nine patients (16%). In five cases the illusion consisted of the transformation of an object into an animal (e.g. a branch was seen as a cat for a few seconds).

Minor hallucinations/illusions occurred in patients on anti-parkinsonian medication in all but one case. One *de novo* patient, a 70-year-old man with no cognitive disorders, had the frequent sensation of an unidentified presence, which he called his 'guardian angel'. Minor hallucinations were static in 53% of the patients. In 27% of the patients they occurred predominantly in the evening or at night, and in 66% of the patients they had no specific schedule. In all cases but one, the sensation was very brief (<5 min, commonly a few seconds) and was rapidly dismissed by nearly all the patients. When the minor hallucinations were isolated (i.e. without other forms of hallucinations, n = 31), they had been present for a mean duration of 0.9 years (SD = 0.7), they were never mentioned spontaneously and they had few, if any, repercussions on the patients (Table 3).

Case 1 (presence hallucinations). A 71-year-old woman had had tremor-predominant Parkinson's disease diagnosed 2 years previously, with no cognitive impairment (MMP score 31). She received levodopa, mianserin and lorazepam for an anxiety disorder. She had daily presence hallucinations for ~6 months before inclusion. The patient lived on her own and had a sister living somewhere else in Paris. During the night or when awakening in the morning, she had the vivid sensation that her sister was lying beside her in the bed. She knew that this was not possible, but she used to lift the top sheet to check that her sister was not there. Later in the morning, when passing near her bed, she often again had the feeling that her sister was there and she checked again. Each episode lasted only a few seconds. In only one instance, 2 months before inclusion, the patient had a brief, formed visual hallucination: she saw two persons in her bedroom, followed them to the living room and then realized they were unreal.

Case 2 (passage hallucination). A 59-year-old man, the owner of a café in Paris, received levodopa and bromocriptine for Parkinson's disease diagnosed 3 years previously. In the evening, while clearing away the tables and chairs, he often had the brief sensation of a mouse passing on the right. He turned his head to the right but could not see anything.

Formed visual hallucinations

Formed visual hallucinations occurred in 48 patients. They had been present for a mean of 2.2 years (SD = 1.8). Formed visual hallucinations consisted of persons, animals and, less often, objects or other entities such as devils or 'Ninja turtles' (Table 4). The hallucinated scenes were kinetic in 47% of cases. Visual hallucinations were more frequent in the evening and during the night in 46% of the patients and had no predominant schedule in 42%. They occurred daily in 29% of the patients, less than daily but at least once a week in 39%, and more rarely in 18%. A single episode of visual hallucinations had occurred (in the 3 months preceding inclusion) in 14% of the patients. The duration of each hallucinatory episode was <5 min in 72% of cases. In patients with diurnal akinetic fluctuations, there was no link between visual hallucinations and 'off' periods except in one case. All the patients with visual hallucinations received dopaminergic treatment, but a modification of the treatment preceding the onset of visual hallucinations was recorded in only 19% of the patients. Visual hallucinations were associated with other types of hallucinations (minor or auditory) in 58% of the patients. Other characteristics of the visual hallucinations and their consequences are summarized in Table 3. Interestingly, insight into the hallucinatory nature of the phenomenon was maintained in all the patients without dementia and 64% of the patients with dementia (corrected $\chi^2 = 5.96$, $P < 0.02$). Associated delusions were present in only 13% of the demented patients and in none of the non-demented patients (not significant). No cases of Capgras syndrome were recorded.

Case 3 (formed visual hallucinations). A 71-year-old man had had Parkinson's disease for 8 years and was taking levodopa. His motor symptoms and signs were mild to moderate and he was independent in all daily activities. However, the patient had developed cognitive disorders about 4 years after the onset of motor symptoms. At the time of inclusion in the study, the MMP score was 18 and the patient met DSM criteria for dementia. Hallucinations had started during a therapeutic trial of a dopaminergic agonist 4 years previously but had not subsided after the agonist was with-

Table 5 *Comparison of patients with formed visual hallucinations and non-hallucinators*

	Patients with visual hallucinations (n = 48) Mean ± SD or %	Non-hallucinators (n =130) Mean ± SD or %	P
Age (years)	73.9 ± 7.0	67.5 ± 9.6	0.0001
Age at onset of Parkinson's disease (years)	61.2 ± 11.0	58.9 ± 10.8	n.s.
Duration of Parkinson's disease (years)	12.9 ± 7.5	8.5 ± 5.6	<0.0001
Males (%)	56.2	56.9	n.s.
Hoehn and Yahr stage in 'on' state	2.5 ± 0.6	1.8 ± 0.8	<0.0001
UPDRS ADL score	15.0 ± 6.3	9.2 ± 5.2	<0.0001
UPDRS motor score in 'on' state	20.8 ± 10.3	14.0 ± 7.6	<0.0001
Axial score	6.0 ± 3.7	3.0 ± 2.5	<0.0001
Akinetic fluctuations (%)	52.1	33.1	0.02
Dyskinesias (%)	50.0	24.6	0.001
CES-D (depression) score	21.9 ± 9.7	17.5 ± 9.2	0.007
MMP (cognitive) score	19.3 ± 6.2	26.9 ± 4.5	<0.0001
Dementia (DSM) (%)	64.6	6.1	<0.0001
Severe sleep disturbances (%)	31.2	18.6	n.s.
Daytime somnolence (%)	70.8	26.9	<0.0001
Ocular pathology (%)	34.0	15.4	0.01
Levodopa daily dose (mg)	700 ± 321	634 ± 428	0.04
Levodopa-equivalent daily dose (mg)	766 ± 365	711 ± 452	n.s.
Treatment with dopamine agonists (%)	41.7	46.2	n.s.
Treatment with anticholinergics (%)	0	10	0.02
Treatment with amantadine (%)	6.2	13	n.s.
Treatment with selegiline (%)	4.2	19.2	0.02

drawn. They consisted of characters which commonly took the form of small incorporeal devils with a blurred face and a changing size. They moved rapidly in 'a sort of haze'. During an episode of lumbar pain, the patient thought that these characters were armed with blades and were 'butchering' his back. However, in most instances, the hallucinations of devils were not frightening and were well tolerated. The patient said that he had become familiar with them, that their lives were now intermingled with his own and that it was like 'living in a fantasy novel' or in a 'parallel world'. The patient repeatedly stated that he was aware of the unreality of the visions, but admitted that he would occasionally speak to them because they 'looked so real'. Visual hallucinations occurred daily, predominantly at night, and the characters seemed to be 'scared' and 'scattered' by light, a noise or a sudden wave of the hand. The patient also experienced presence hallucinations: 'it's a presence behind me; I try to catch it by turning round but I never see its face'.

Auditory hallucinations

Auditory hallucinations occurred in 21 patients but were isolated (i.e. the hallucination consisted only of auditory phenomena) in only five cases (2.3% of the patients). In most cases, auditory hallucinations were combined with visual hallucinations, either at different moments or simultaneously (in seven cases), like the sound-track of the scene (e.g. hallucinated persons were heard speaking). They could also be combined with presence hallucinations. Auditory hallucinations were verbal in 13 cases (62%), musical in three (14%) and consisted of various other noises (often the sound of steps) in 11 patients (48%). Deafness was present in two cases of musical hallucinations.

Case 4 (auditory hallucination). A 68-year-old-woman had received a diagnosis of Parkinson's disease 18 years previously. She was taking levodopa, bromocriptine, piribedil and amantadine. She had moderate cognitive disorders (MMP score 25) and felt depressed. She had experienced presence hallucinations (of an unindentified person) for the last 6 months. In one instance she saw her deceased son with another person. Her son distinctly said to her: 'take care of yourself'.

Comparison of hallucinators and non-hallucinators

The patients with isolated minor hallucinations (n = 31) were compared with the patients with no hallucinations (n = 130). The only significant difference was a higher CES-D score (corresponding to more depressive symptoms) in the group with minor hallucinations (21.9 ± 9.5 versus 17.5 ± 9.2, P = 0.02). When the presence of depression was determined using the cut-off values of the CES-D, depression was more frequent in the patients with minor hallucinations (50%) than in the patients without any hallucinations (34%), but this difference did not reach significance.

The patients with formed visual hallucinations (n = 48) are compared with the non-hallucinators (n = 130) in Table 5.

Table 6 *Factors predictive of formed visual hallucinations (multivariate non-conditional logistic regression)*

	Odds ratio (95% confidence interval)	*P*
Severe cognitive disorder (MMP <24)	10.3 (4.3–25.1)	<0.0001
Daytime somnolence	3.5 (1.4–5.0)	0.006
Duration of Parkinson's disease >8.0 years	3.1 (1.3–7.6)	0.01

Patients with visual hallucinations differed in a number of respects: they were older, had a longer duration of disease, had a more severe motor state, had more depressive symptoms, and were more likely to have cognitive impairment, day-time somnolence and a history of ocular pathology. They were less likely to receive anticholinergics or selegiline and received a higher daily dose of levodopa, but the levodopa-equivalent dose did not differ significantly between the two groups. Visual hallucinations were recorded in 70% of the patients with dementia ($n = 44$) versus 10% of non-demented patients ($P < 0.001$), and in 55% of the patients with severe cognitive disorders (MMP score <24, $n = 65$) versus 8% of the patients with absent or moderate cognitive impairment ($P < 0.001$).

The patients with hallucinations of any type ($n = 86$) were compared with the patients with no hallucinations. The results were identical to those of the preceding analysis, except for the degrees of significance (data not shown).

A multivariate analysis was applied to the data on formed visual hallucinations. Three independent factors predictive of visual hallucinations were identified: the presence of severe cognitive disorders, as defined by a MMP score <24; the presence of daytime somnolence; and a disease duration longer than the median (8 years) (Table 6).

Visual hallucinations according to the duration of Parkinson's disease

The prevalence of hallucinations of all types and of visual hallucinations in the 3 months preceding inclusion in the study increased with the duration of Parkinson's disease (Fig. 1). We compared the characteristics of the patients with and without hallucinations among those with a short history of Parkinson's disease (≤5 years, $n = 65$) and those with a long history (>5 years, $n = 151$). The results are shown in Table 7. Visual hallucinations had been present for a mean of 0.8 years (SD = 0.3) in the patients with short-duration Parkinson's disease and for 2.4 years (SD = 1.8) in the patients with long-duration Parkinson's disease ($P = 0.03$). However, eight patients with long-duration Parkinson's disease ($n = 42$) and one patient with short-duration Parkinson's disease ($n = 6$) could not remember the year of onset of visual hallucinations. In both groups, patients with formed visual hallucinations were older and were more likely to be demented, according to DSM criteria, than non-hallucinators. The MMP score was lower in patients with visual hallucinations, although the difference reached significance only in patients with long-duration Parkinson's disease. Patients with visual hallucinations had a more severely affected motor state than non-hallucinators in the long-duration group only.

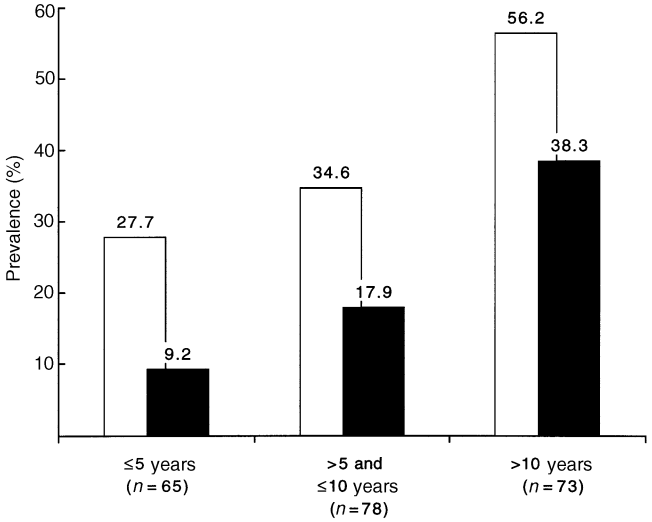

Fig. 1 Prevalence (%) of hallucinations of all types (white bars) and of formed visual hallucinations (black bars) according to the duration of Parkinson's disease.

Discussion

Prevalence

Only prospective studies should be taken into account when discussing the prevalence of hallucinations during the course of Parkinson's disease, because of the low frequency of self-reported hallucinations. This low frequency is explained by the ease with which a number of hallucinations are tolerated and by the fear of some patients of being considered insane. In the only population-based study of psychotic symptoms in Parkinson's disease, the frequency of hallucinations and delusions during the week before evaluation was found to be 16% (Aarsland *et al.*, 1999). The results of recent prospective studies of hallucinations in outpatients with Parkinson's disease are summarized in Table 8. The present study and two other studies gave similar figures for the prevalence of visual hallucinations (22.2–25.7%) (Sanchez-Ramos *et al.*, 1996; Graham *et al.*, 1997). Similarly, Pappert and colleagues found that 26% of outpatients with Parkinson's disease had hallucinations or illusions (Pappert *et al.*, 1999). The higher prevalence in one study (Inzelberg *et al.*, 1998) might be due to the older patient population involved. Interestingly, the rate of auditory hallucinations was similar in three studies (~10%), while only one group recorded none. In the present study the total prevalence rate of hallucinations in the 3 months before inclusion was nearly 40%. This high

Table 7 *Comparison of patients with and without formed visual hallucinations according to the duration (⩽5 versus >5 years) of Parkinson's disease*

	Duration of Parkinson's disease ⩽5 years (n = 65)			Duration of Parkinson's disease >5 years (n = 151)		
	Patients with visual hallucinations (n = 6)	Non-hallucinators (n = 47)	P	Patients with visual hallucinations (n = 83)	Non-hallucinators	P
Age (years)	75.8 ± 7.7	65.8 ± 10.6	0.04	73.6 ± 7.0	68.4 ± 8.9	0.002
Age at onset of Parkinson's disease (years)	71.8 ± 7.9	62.2 ± 11.0	0.04	59.6 ± 10.6	57.1 ± 10.3	n.s.
Males (%)	0	55.3	0.02	64.3	57.8	n.s.
Hoehn and Yahr stage in 'on' state	2.4 ± 1.1	1.6 ± 0.8	n.s.	2.6 ± 0.5	2.0 ± 0.8	<0.001
UPDRS ADL score	11.3 ± 5.6	7.0 ± 4.9	n.s.	15.6 ± 6.2	10.3 ± 5.0	<0.001
UPDRS motor score in 'on' state	22.5 ± 14.5	11.6 ± 6.6	0.02	20.5 ± 9.7	15.3 ± 7.9	0.004
Axial score	3.2 ± 2.2	2.2 ± 2.5	n.s.	6.4 ± 3.7	3.5 ± 2.5	<0.001
Akinetic fluctuations (%)	17	11	n.s.	57	46	n.s.
Dyskinesias (%)	0	8	n.s.	57	34	0.02
CES-D (depression) score	20.0 ± 6.0	16.4 ± 8.3	n.s.	22.1 ± 10.0	18.1 ± 9.7	0.04
MMP (cognitive) score	22.3 ± 6.7	27.4 ± 3.6	n.s.	18.8 ± 6.1	26.6 ± 4.9	<0.001
Dementia (DSM) (%)	50	2	<0.001	67	8	<0.001
Severe sleep disturbances (%)	50	15	n.s.	29	21	n.s.
Daytime somnolence (%)	17	19	n.s.	79	31	<0.001
Ocular pathology (%)	17	13	n.s.	36	17	0.02
Levodopa daily dose (mg)	367 ± 154	408 ± 185	n.s.	748 ± 310	728 ± 465	n.s.
Levodopa-equivalent daily dose (mg)	367 ± 154	431 ± 204	n.s.	823 ± 351	827 ± 477	n.s.
Treatment with dopamine agonists (%)	0	23	n.s.	48	59	n.s.
Treatment with anticholinergics (%)	0	6	n.s.	0	12	0.02
Treatment with amantadine (%)	0	8	n.s.	7	16	n.s.
Treatment with selegiline (%)	0	23	n.s.	5	17	0.04

Table 8 *Reported prevalence of hallucinations in Parkinson's disease (prospective studies)*

	n	Total prevalence (%)	Visual hallucinations (%)	Auditory hallucinations (%) [isolated]	Study period
Sanchez-Ramos *et al*. (1996)	214	25.7	25.7	0	?
Graham *et al*. (1997)	129	24.8	23.2	11.6 [1.5]	Past and present
Inzelberg *et al.* (1998)	121	37	37	8 (0)	Past and present
This study	216	39.8	22.2 (formed)	9.7 [2.3]	3 months preceding inclusion

figure was obtained when minor forms of hallucinations were taken into account.

Phenomenology

To our knowledge, presence and passage hallucinations have not been studied systematically in Parkinson's disease until now, although presence hallucinations have been mentioned by other investigators (Sanchez-Ramos *et al.*, 1996). Presence hallucinations were the most common type in our series. Passage hallucinations and illusions are visual phenomena, but presence hallucinations cannot be related to a specific sensory modality, although they were often described by the patients in terms referring to imagery (e.g. 'the image is behind me'). Presence hallucinations have been described previously in other conditions, such as narcolepsy (Ribstein, 1976) and bereavement (Rees, 1971; Grimby, 1993).

The formed visual hallucinations recorded in this study were similar to those described previously in patients with Parkinson's disease (Factor *et al*., 1995; Sanchez-Ramos *et al.*, 1996; Graham *et al.*, 1997), consisting in most cases of rather simple and non-threatening images of people or animals. Lack of insight and associated delusions were present only in some patients with dementia. When auditory verbal hallucinations were present, they were

always neutral and clearly different from the pejorative or threatening auditory hallucinations characteristic of schizophrenia.

Predictive factors and pathophysiology

Minor hallucinations/illusions

Patients with isolated minor hallucinations/illusions differed from patients without hallucinations only by the presence of more depressive symptoms on the CES-D rating scale, suggesting that depressive symptoms are a facilitating factor. Indeed, depression may sometimes trigger or aggravate hallucinations associated with deafness or ocular pathology (Fénelon *et al.*, 1993). However, when we analysed depression according to CES-D cut-off scores, the difference between the Parkinson's disease patients with minor hallucinations/illusions and those with no hallucinations was not significant. Interestingly, hallucinations involving the deceased spouse (sense of a presence, and visual or auditory hallucinations) have been reported in up to half of widowed persons, with a higher frequency in the elderly (Rees, 1971; Grimby, 1993). In the present study, the 'presence' was that of a deceased relative in only three cases (8% of the presence hallucinations); bereavement cannot therefore explain the bulk of the cases.

Minor hallucinations may be a non-specific side-effect of antiparkinsonian drugs. However, one of the patients with a vivid presence hallucination was receiving no treatment. An alternative possibility is, therefore, that minor hallucinations/illusions are due to the disease itself, whatever its form and duration. Presence hallucinations might arise from a conflict between a preconscious visual perception (hallucinated) and actual normal vision. Passage hallucinations are very brief and are localized in the periphery of the visual field, and they are usually identified as a person or an animal of a particular species. These characteristics suggest that passage hallucinations could arise from the misinterpretation of a very flimsy perception due to disinhibition of an early part of the visual cognitive process, such as the perceptual representation system. This system has been implicated by Tulving and Schacter in the priming effects on so-called data-driven implicit memory (Tulving and Schacter, 1990). The system works at a presemantic level and accelerates the recognition of previously encountered stimuli from very slight cues. Patients with Parkinson's disease have been reported to have an impairment in the process of ignoring irrelevant stimuli (Downes *et al.*, 1989). Thus, passage hallucinations, and possibly other forms of minor hallucinations and illusions, could be rooted in false recognition proposed by the perceptual representation system in response to very flimsy stimuli. A depressed mood could play a part by decreasing attentional resources and the ability to inhibit irrelevant recognition.

Dopaminergic agents and other treatments

The hallucinations of Parkinson's disease are commonly considered to be a side-effect of dopaminergic therapy (Friedman, 1991; Factor *et al.*, 1995). This point of view is supported by several arguments. First, 'psychotic' reactions were commonly recorded at the beginning of the levodopa era. Secondly, all the dopaminergic agents used in the treatment of Parkinson's disease may elicit adverse psychotic reactions, there being a greater incidence with dopamine receptor agonists than with levodopa (Saint-Cyr *et al.*, 1993). Thirdly, in Parkinson's disease, 'psychotic' symptoms may be reduced by a decrease in or cessation of dopaminergic treatment (Friedman, 1991; Mendis *et al.*, 1996). In some cases, hallucinations disappeared after a 'drug holiday' and had not recurred after 1 year (Koller *et al.*, 1981).

However, other evidence indicates that hallucinations are not a simple dopaminergic adverse event. First, in early reports the frequency of acute psychic adverse reactions may have been overestimated as larger doses of levodopa were used (Manford and Andermann, 1998). Moreover, as stressed by Factor and colleagues, 'it is difficult to determine the incidence with which these problems occurred because the early studies varied with regard to the inclusion criteria, the dosages of levodopa employed, and the classification of the psychiatric effects reported' (Factor *et al.*, 1995). In fact, hallucinations in the course of Parkinson's disease usually occur in a normal state of consciousness without delirium, and have a chronic course (Goetz *et al*., 1998*a*, *b*; Pappert *et al.*, 1998). In our study, only two (2.3%) of the 86 patients with recent hallucinations of any type fulfilled DSM-IV criteria for delirium, and a recent change in antiparkinsonian drug dosage was found in only 19% of the patients with visual hallucinations. Secondly, hallucinations were recorded before the use of levodopa (de Ajuriaguerra, 1971; Rondot *et al.*, 1984), but the data are difficult to interpret because most studies were not prospective, patients with postencephalitic syndromes were often included, and anticholinergic medications were used widely. Thirdly, there is no simple dose–effect relationship between dopaminergic treatment and the development of hallucinations. In the present study, the daily dose of levodopa but not the daily levodopa-equivalent dose was significantly higher in patients with visual hallucinations. However, this variable did not emerge as an independent predictive factor in the multivariate analysis. Moreover, in two prospective studies (Sanchez-Ramos *et al.*, 1996; Graham *et al.*, 1997) and one retrospective study (Shergill *et al*., 1998), hallucinations were not associated with the dosage of dopaminergic medication (levodopa or dopaminergic agonists). Recently, Goetz and colleagues showed that there was not a simple relationship between visual hallucinations and high plasma levels of levodopa or sudden changes in plasma levels (Goetz *et al.*, 1998). This does not preclude a facilitating or triggering action of dopaminergic treatment on hallucinations, but eliminates a simple dose-related side-effect. Fourthly, non-dopaminergic pharmacological agents (mainly anticholinergics) may elicit hallucinations in Parkinson's disease patients (Saint-Cyr *et al.*, 1993). Fifthly, in a series of patients treated with dopamine agonists for pituitary tumours, hallucinations (mainly auditory) occurred in only

1% of cases (Turner *et al.*, 1984). Finally, hallucinations may occur spontaneously (i.e. in the absence of dopaminergic or other treatment), sometimes at presentation, in the course of DLB (dementia with Lewy bodies) (Ala *et al.*, 1997; Ballard *et al.*, 1999). As in Parkinson's disease, hallucinations in DLB are typically recurrent formed visual hallucinations (McKeith *et al.*, 1996). DLB may be clinically and pathologically difficult to distinguish from Parkinson's disease with dementia, and the boundaries between the two conditions are blurred (McKeith *et al.*, 1996). It is therefore likely that the hallucinations of Parkinson's disease (more frequent when dementia is present) and the hallucinations of DLB share mechanisms that are distinct from a side-effect of treatment.

In the present study, non-hallucinators were more likely to be on anticholinergics or selegiline than patients with hallucinations. A similar paradoxical, negative association between anticholinergics and hallucinations was found by Sanchez-Ramos and colleagues (Sanchez-Ramos *et al.*, 1996). This reflects the recommendation whereby the use of these drugs in patients with cognitive impairment is avoided because of the well-known risk of cognitive worsening and/or hallucinations in this population.

Cognitive impairment

We found that severe cognitive disorders were a major and independent predictive factor for visual hallucinations. In other prospective studies, cognitive impairment was significantly more frequent in Parkinson's disease patients with visual hallucinations, whether cognition was studied using the Folstein Mini-Mental State Examination (Sanchez-Ramos *et al.*, 1996; Aarsland *et al.*, 1999), the Blessed dementia scale (Graham *et al.*, 1997) or the 'short mental test' (Inzelberg *et al.*, 1998). In a study of Parkinson's disease patients with dementia, 36% of the patients had hallucinations and/or delusions, and the Mini-Mental State Examination score was a significant predictor of these symptoms (Naimark *et al.*, 1996). In the present study, 70% of the patients with dementia (according to DSM criteria) had visual hallucinations. It is possible that the prevalence of hallucinations in demented Parkinson's disease patients is underestimated, as visual hallucinations are rarely reported spontaneously and their presence is difficult to ascertain when the dementia is severe.

Hallucinations, mostly visual, may occur in the course of degenerative dementias other than Parkinson's disease-associated dementia. We have already mentioned DLB, where hallucinations are present in up to 70% of patients (Perry *et al.*, 1995). Visual hallucinations are also reported in up to 25% of patients with Alzheimer's disease (Ballard *et al.*, 1999) and in patients with frontotemporal dementia linked to chromosome 17 (Foster *et al.*, 1997). In all these conditions, as emphasized in DLB, hallucinations may occur in the absence of any pharmacological facilitating factor.

It is not clear whether cognitive changes and hallucinations have a causative link or are independent consequences of the pathological processes. On the one hand, impaired judgement, which is the hallmark of dementia, could lead to misinterpretation of sensory stimuli. It could also be responsible for the lack of insight into the hallucinations and the presence of associated delusions, as in our study these features were present only in the patients with severe cognitive disorders. On the other hand, visual hallucinations could also be generated by an impairment in the processing of the visual stimuli in the visual association cortices. Such a mechanism has been suggested to facilitate visual hallucinations in the course of Alzheimer's disease (Holroyd and Sheldon-Keller, 1995). Although the nature and pathophysiology of the changes are controversial, it is generally assumed that Parkinson's disease patients have deficits in visuospatial abilities, which progress as a function of advancing motor disease and the severity of dementia (Mohr *et al.*, 1995). Poor visuospatial performance also appears to be characteristic of DLB when patients with this disease are compared with Alzheimer's disease patients (Shimomura *et al.*, 1998). Interestingly, studies using PET have shown marked occipital hypometabolism in Parkinson's disease patients with dementia (Vander Borght *et al.*, 1997) and in patients with DLB (Albin *et al.*, 1996). Proposed mechanisms include diaschisis due to disruption of intracortical connections (Albin *et al.*, 1996) and an occipital cholinergic deficit secondary to the degenerative processes in the basal nucleus of Meynert (Shimomura *et al.*, 1998). The more frequent involvement of the visual cortex in Parkinson's disease dementia and DLB than in Alzheimer's disease could explain the higher prevalence of visual hallucinations in the first two conditions. Another possibility is that the prevalence of hallucinations is modified in different ways by pharmacological factors, i.e. it may be enhanced by dopaminergic agents in Parkinson's disease and reduced by neuroleptics in Alzheimer's disease.

Sleep–wake disturbances

We found that day-time somnolence, but not severe sleep disorders, was an independent predictive factor for visual hallucinations. Moreover, we and others (Fernandez *et al.*, 1992; Sanchez-Ramos *et al.*, 1996) have found that hallucinations in Parkinson's disease are more frequent in the evening and during the night, a feature shared by other forms of hallucinosis (e.g. peduncular hallucinosis and Charles Bonnet syndrome) and which is more likely to be due to alteration of arousal than to darkness (Manford and Andermann, 1998). The association between hallucinations and sleep–wake disturbances in Parkinson's disease was first stressed by Moskovitz and colleagues, who suggested that the symptoms progressed from vivid dreams to hallucinations, to delusions and finally to a confused state, this progression being due to a 'kindling' mechanism secondary to chronic dopatherapy (Moskovitz *et al.*, 1978). Other investigators have also found a strong association between the psychiatric side-effects of levodopa and sleep disruption, and have suggested that sleep disruption is an early feature of 'levodopa psychosis'

(Nausieda *et al.*, 1982). Recently, Pappert and colleagues showed that 82% of Parkinson's disease patients with hallucinations had some form of sleep disorder (Pappert *et al.*, 1999). However, the authors found a close association between hallucinations and altered dream phenomena but not sleep fragmentation. It should be emphasized that sleep disturbances are frequent in the course of Parkinson's disease, even in the absence of hallucinations, and data from clinical studies do not allow one to conclude that sleep disturbances as a whole and hallucinations are on a continuum and share a common pathophysiological mechanism. In this regard, polysomnographic studies comparing Parkinson's disease patients with and without hallucinations could be valuable. We are aware of only one such study, which included five patients in each group (Comella *et al.*, 1993). Compared with non-hallucinators, patients with hallucinations had a lower sleep efficiency, a reduced total REM (rapid eye movement) sleep time and a reduced REM percentage. These findings suggest a link between REM sleep abnormalities and the development of hallucinations during the course of Parkinson's disease. An association between a disturbance of the sleep–wake cycle and hallucinations occurs in other conditions, such as narcolepsy and peduncular hallucinosis. Lhermitte stressed similarities between dreams and peduncular hallucinosis and suggested that, in the latter condition, hallucinations might arise from a dysfunction of sleep–wake mechanisms secondary to the peduncular lesion (Lhermitte, 1922). Accordingly, lesions in Parkinson's disease might involve brainstem structures controlling sleep, especially those generating REM sleep (Manford and Andermann, 1998).

Motor status

Previous studies showed that Parkinson's disease patients with hallucinations were more disabled than non-hallucinators (Sanchez-Ramos *et al.*, 1996; Barclay *et al.*, 1997; Graham *et al.*, 1997). We also found that motor status was more severely affected in hallucinators than in non-hallucinators but did not emerge as a factor predictive of visual hallucinations in multivariate analysis. This could be due to the correlation of motor impairment with the duration of the disease, the latter remaining a predictive factor in the multivariate analysis. In patients with fluctuating symptoms, we did not confirm the finding of Fernandez and colleagues that patients commonly experience hallucinations only while in the 'off' state (Fernandez *et al.*, 1992).

Depression

We found that patients with formed visual hallucinations had a higher CES-D score than patients without hallucinations, but this score was not a predictive factor in the multivariate analysis. Recent prospective studies gave conflicting results about the link between hallucinations and depression in Parkinson's disease. Hallucinators were found to have a history of depression more frequently (Sanchez-Ramos *et al.*, 1996) or to have a higher score than non-hallucinators on the Montgomery and Åsberg Depression Rating Scale (Aarsland *et al.*, 1999). In another study (Graham *et al.*, 1997), hallucinators with a disease duration >5 years had fewer depressive symptoms (as assessed by the Beck Depressive Inventory) than non-hallucinators. Conversely, a higher 'thought disorder' score (an item of the UPDRS which includes hallucinations) was predictive of major depression in a study of risk factors for depression in Parkinson's disease (Tandberg *et al.*, 1997). The relationship between hallucinations and depression thus remains unclear.

Ocular disorders

Visual hallucinations may occur in blind patients and in as many as 12% of cognitively normal people with poor visual acuity, a condition called the Charles Bonnet syndrome (Teunisse *et al.*, 1996). Moreover, it has been shown that decreased visual acuity is a risk factor for the presence of visual hallucinations in patients with Alzheimer's disease (Holroyd and Sheldon-Keller, 1995; McShane *et al.*, 1995). Patients with Parkinson's disease may have a coincidental age-related ocular pathology responsible for visual deterioration, facilitating the development of visual hallucinations. In the present study, patients with visual hallucinations were more likely to have a known ocular disorder, but such disorders did not emerge as an independent predictive factor. This does not eliminate the possibility that ophthalmological abnormalities facilitate the development of visual hallucinations, at least in some patients with Parkinson's disease. Interestingly, visual hallucinations in the Charles Bonnet syndrome share some features with those occurring in the course of Parkinson's disease. They include a wide variety of images, all patients being aware of the unreal nature of the hallucinations and most not suffering as a result. Visual hallucinations in Charles Bonnet syndrome are also more frequent in the evening or at night, suggesting that both sensory deprivation and a low level of arousal are facilitating factors (Teunisse *et al.*, 1996; Manford and Andermann, 1998).

Specific, non-coincidental visual factors may also intervene in the genesis of the hallucinations in Parkinson's disease. Patients with Parkinson's disease have subtle visual disturbances related to the disease, including abnormalities in spatiotemporal contrast sensitivity and in colour discrimination. These changes have been ascribed to a retinal dopaminergic deficiency (Bodis-Wollner, 1990; Büttner *et al.*, 1995). The possible role of disease-related visual impairment in Parkinson's disease has been investigated by Diederich and colleagues, who found that, in Parkinson's disease patients with normal acuity, those with visual hallucinations had significantly worse performances in tests assessing colour vision and contrast discrimination (Diederich *et al.*, 1998). Another study has suggested an association between distorted chromatic contour perception and the presence of visual

hallucinations in patients with Parkinson's disease (Büttner *et al.*, 1996). Therefore, coincidental ocular pathology or more subtle visual disturbances associated with Parkinson's disease may be facilitating factors for visual hallucinations.

Hallucinations according to the duration of the disease

We found that the prevalence of hallucinations of all types and of visual hallucinations in the 3 months preceding inclusion in the study increased with the duration of the disease. Moreover, the duration of Parkinson's disease (and not the age at onset or at inclusion) was an independent predictor of visual hallucinations in the multivariate analysis. Other studies gave conflicting results on the relationship between hallucinations and disease duration. In a retrospective study of 100 patients, logistic regression analysis also showed an association between 'psychosis' (mainly hallucinations) and an increased duration of the disease (Shergill *et al.*, 1998). An association between the duration of the disease and the occurrence of hallucinations was also found by some investigators (Sanchez-Ramos *et al.*, 1996; Barclay *et al.*, 1997) but not by others (Tanner *et al.*, 1983).

Graham and colleagues found a peak in the onset of hallucinations during the first 5 years of the disease, superimposed on an increasing frequency of onset of hallucinations as the duration of the disease increased (Graham *et al.*, 1997). In their study, hallucinations were associated with more frequent fluctuations and dyskinesias, but not with cognitive impairment, in 'early' hallucinators (disease duration of $\leqslant$5 years), while in 'late' hallucinators the hallucinations were associated with loss of balance and global cognitive impairment. Our results cannot be compared directly with those of Graham and colleagues because we took into account the crude prevalence of hallucinations according to the duration of the disease, and not the prevalence of onset of hallucinations. The reason for this choice was that, in many cases, especially when cognitive impairment was present, patients could not remember the date of onset of the hallucinations or gave responses which did not appear to be reliable. Another important difference is that the patients in all the groups studied by Graham and colleagues were younger at the onset of Parkinson's disease than the patients in our study (for instance, 62.3 $\pm$ 8.8 years versus 71.8 $\pm$ 7.9 years for the early hallucinator groups). In the present study, dementia was more frequent and MMP scores were lower in patients with visual hallucinations whether the duration of the disease was longer or shorter than 5 years. However, in the short-duration group, the difference in MMP score did not reach statistical significance, possibly because of the small size of the group of patients with visual hallucinations. We did not find any characteristics suggestive of a more rapid progression of motor symptoms in the group of patients with visual hallucinations and short-duration Parkinson's disease.

In conclusion, we found that, when including minor hallucinations/illusions, hallucinatory phenomena in Parkinson's disease are more frequent than has been described previously: the total prevalence of hallucinatory phenomena in the 3 months preceding inclusion was nearly 40%, and the lifetime prevalence, which was possibly underestimated, was 46%. Although they were frequent, hallucinatory phenomena required a specific therapeutic change in only a minority of cases. This study dismisses a monofactorial view of the pathophysiology of hallucinations in Parkinson's disease, in which the hallucinations are a simple dose-related side-effect of dopaminergic treatment. Rather, pharmacological agents, cognitive impairment, sleep–wake cycle disturbances, and possibly other factors related to the duration of the disease, seem to act as cofactors in the genesis of hallucinations. Additional factors, such as depression and visual disturbances, may contribute to the development (and/or influence the content) of the hallucinations, but their potential role has to be investigated further.

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References

Aarsland D, Larsen JP, Cummings JL, Laake K. Prevalence and clinical correlates of psychotic symptoms in Parkinson disease. A community-based study. Arch Neurol 1999; 56: 595–601.

Ala TA, Yang KH, Sung JH, Frey WH 2nd. Hallucinations of parkinsonism help distinguish patients with dementia and cortical Lewy bodies from patients with Alzheimer's disease at presentation: a clinicopathological study. J Neurol Neurosurg Psychiatry 1997; 62: 16–21.

Albin RL, Minoshima S, D'Amato CJ, Frey KA, Kuhl DA, Sima AA. Fluoro-deoxyglucose positron emission tomography in diffuse Lewy body disease. Neurology 1996; 47: 462–6.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV. 4th ed. Washington (DC): American Psychiatric Association; 1994.

Ballard C, Holmes C, McKeith I, Neill D, O'Brien J, Cairns N, et al. Psychiatric morbidity in dementia with Lewy bodies: a prospective clinical and neuropathological comparative study with Alzheimer's disease. Am J Psychiatry 1999; 156: 1039–45.

Barclay CL, Hildebrand K, Gray P, Mendis T, Mohr E, Grimes JD. Risk factors for the development of psychosis in Parkinson's disease [abstract]. Mov Disord 1997; 12 Suppl 1: 108.

Bodis-Wollner I. Visual deficits related to dopamine deficiency in experimental animals and Parkinson's disease patients. [Review]. Trends Neurosci 1990; 13: 296–302.

Büttner T, Kuhn W, Müller T, Patzold T, Heidbrink K, Przuntek H. Distorted color discrimination in 'de novo' parkinsonian patients. Neurology 1995; 45: 386–7.

Büttner T, Kuhn W, Müller T, Welter FL, Federlein J, Heidbrink K, et al. Visual hallucinosis: the major clinical determinant of distorted chromatic contour perception in Parkinson's disease. J Neural Transm 1996; 103: 1195–204.

Comella CL, Tanner CM, Ristanovic RK. Polysomnographic sleep measures in Parkinson's disease patients with treatment-induced hallucinations. Ann Neurol 1993; 34: 710–4.

Cummings JL. Managing psychosis in patients with Parkinson's disease [editorial]. N Engl J Med 1999; 340: 801–3.

de Ajuriaguerra J. Etude psychopathologique des parkinsoniens. In: de Ajuriaguerra J, Gauthier G, editors. Monoamines, noyaux gris centraux et syndrome de Parkinson. Genève: Masson; 1971. p. 327–55.

Diederich NJ, Goetz CG, Raman R, Pappert EJ, Leurgans S, Piery V. Poor visual discrimination and visual hallucinations in Parkinson's disease. Clin Neuropharmacol 1998; 21: 289–95.

Downes JJ, Roberts AC, Sahakian BJ, Evenden JL, Morris RG, Robbins TW. Impaired extra-dimensional shift performance in medicated and unmedicated Parkinson's disease: evidence for a specific attentional dysfunction. Neuropsychologia 1989; 27: 1329–49.

Factor SA, Molho ES, Podskalny GD, Brown D. Parkinson's disease: drug-induced psychiatric states. [Review]. Adv Neurol 1995; 65: 115–38.

Fahn S, Elton RL, the UPDRS Development Committee. Unified Parkinson's Disease Rating Scale. In: Fahn S, Marsden CD, Calne D, Goldstein M, editors. Recent developments in Parkinson's disease, Vol. 2. Florham Park: Macmillan Healthcare Information; 1987. p. 153–63.

Fénelon G, Marie S, Ferroir JP, Guillard A. Hallucinose musicale: 7 cas. Rev Neurol (Paris) 1993; 149: 462–7.

Fernandez W, Stern G, Lees AJ. Hallucinations and parkinsonian motor fluctuations. Behav Neurol 1992; 5: 83–6.

Foster NL, Wilhelmsen K, Sima AA, Jones MZ, D'Amato CJ, Gilman S. Frontotemporal dementia and parkinsonism linked to chromosome 17: a consensus conference. [Review]. Ann Neurol 1997; 41: 706–15.

Friedman JH. The management of the levodopa psychoses. [Review]. Clin Neuropharmacol 1991; 14: 283–95.

Fuhrer R, Rouillon F. La version française de l'échelle CES-D (Center for Epidemiologic Studies—Depression scale). Description et traduction de l'échelle d'auto-évaluation. Psychiatrie Biol 1989; 4: 163–6.

Goetz CG, Stebbins GT. Risk factors for nursing home placement in advanced Parkinson's disease. Neurology 1993; 43: 2227–9.

Goetz CG, Stebbins GT. Mortality and hallucinations in nursing home patients with advanced Parkinson's disease. Neurology 1995; 45: 669–71.

Goetz CG, Pappert EJ, Blasucci LM, Stebbins GT, Ling ZD, Nora MV, et al. Intravenous levodopa infusions in hallucinating Parkinson's disease patients: high-dose challenge does not precipitate hallucinations. Neurology 1998a; 50: 515–7.

Goetz CG, Vogel C, Tanner CM, Stebbins GT. Early dopaminergic drug-induced hallucinations in parkinsonian patients. Neurology 1998b; 51: 811–4.

Graham JM, Grünewald RA, Sagar HJ. Hallucinosis in idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 1997; 63: 434–40.

Grimby A. Bereavement among elderly people: grief reactions, post-bereavement hallucinations and quality of life. Acta Psychiatr Scand 1993; 87: 72–80.

Holroyd S, Sheldon-Keller A. A study of visual hallucinations in Alzheimer's disease. J Am Geriatr Soc 1995; 3: 198–205.

Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992; 55: 181–4.

Inzelberg R, Kipervasser S, Korczyn AD. Auditory hallucinations in Parkinson's disease. J Neurol Neurosurg Psychiatry 1998; 64: 533–5.

Koller WC, Weiner WJ, Perlik S, Nausieda PA, Goetz CG, Klawans HL. Complications of chronic levodopa therapy: long-term efficacy of drug holiday. Neurology 1981; 31: 473–6.

Krack P, Pollak P, Limousin P, Hoffmann D, Xie J, Benazzouz A, et al. Subthalamic nucleus or internal pallidal stimulation in young onset Parkinson's disease. Brain 1998; 121: 451–7.

Langston JW, Widner H, Goetz CG, Brooks D, Fahn S, Freeman T, et al. Core assessment program for intracerebral transplantations (CAPIT). Mov Disord 1992; 7: 2–13.

Lhermitte J. Syndrome de la calotte du pédoncule cérébral. Les troubles psycho-sensoriels dans les lésions du mésencéphale. Rev Neurol (Paris) 1922; 38: 1359–65.

Mahieux F, Michelet D, Manifacier MJ, Boller F, Fermanian J, Guillard A. Mini-mental Parkinson: first validation study of a new bedside test constructed for Parkinson's disease. Behav Neurol 1995; 8: 15–22.

Mahieux F, Fénelon G. Prévalence des troubles neuropsychologiques au cours de la maladie de Parkinson. In: Gely-Nargeot MC, Ritchie K, Touchon J, editors. Actualités 1998 sur la maladie d'Alzheimer et les syndromes apparentés. Marseilles: Solal; 1998. p. 457–66.

Mahieux F, Fénelon G, Flahault A, Manifacier MJ, Michelet D, Boller F. Neuropsychological prediction of dementia in Parkinson's disease. J Neurol Neurosurg Psychiatry 1998; 64: 178–83.

Manford M, Andermann F. Complex visual hallucinations. Clinical and neurobiological insights. [Review]. Brain 1998; 121: 1819–40.

McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy body (DLB): report of the consortium on DLB international workshop. [Review]. Neurology 1996; 47: 1113–24.

McShane R, Gedling K, Reading M, McDonald B, Esiri MM, Hope T. Prospective study of relations between cortical Lewy bodies, poor eyesight, and hallucinations in Alzheimer's disease. J Neurol Neurosurg Psychiatry 1995; 59: 185–8.

Meco G, Bonifati V, Cusimano G, Fabrizio E, Vanacore N. Hallucina-

tions in Parkinson disease: neuropsychological study. Ital J Neurol Sci 1990; 11: 373–9.

Mendis T, Barclay CL, Mohr E. Drug-induced psychosis in Parkinson's disease. A review of management. CNS Drugs 1996; 5: 166–74.

Mohr E, Mendis T, Grimes JD. Late cognitive changes in Parkinson's disease with an emphasis on dementia. [Review]. Adv Neurol 1995; 65: 97–113.

Moskovitz C, Moses H 3d, Klawans HL. Levodopa-induced psychosis: a kindling phenomenon. Am J Psychiatry 1978; 135: 669–75.

Naimark D, Jackson E, Rockwell E, Jeste DV. Psychotic symptoms in Parkinson's disease patients with dementia. J Am Geriatr Soc 1996; 44: 296–9.

Nausieda PA, Weiner WJ, Kaplan LR, Weber S, Klawans HL. Sleep disruption in the course of chronic levodopa therapy: an early feature of the levodopa psychosis. Clin Neuropharmacol 1982; 5: 183–94.

Pappert EJ, Goetz CG, Raman R, Pass M, Leurgans S. Stability of hallucinations and illusions in Parkinson's disease: 18-month prospective study [abstract]. Mov Disord 1998; 13 Suppl 2: 90.

Pappert EJ, Goetz CG, Niederman FG, Raman R, Leurgans S. Hallucinations, sleep fragmentation, and altered dream phenomena in Parkinson's disease. Mov Disord 1999; 14: 117–21.

Perry EK, Perry RH. Acetylcholine and hallucinations: disease-related compared to drug-induced alterations in human consciousness. [Review]. Brain Cogn 1995; 28: 240–58.

Pillon B, Dubois B, Cusimano G, Bonnet AM, Lhermitte F, Agid Y. Does cognitive impairment in Parkinson's disease result from non-dopaminergic lesions? J Neurol Neurosurg Psychiatry 1989; 52: 201–6.

Rees WD. The hallucinations of widowhood. Br Med J 1971; 4: 37–41.

Ribstein M. Hypnagogic hallucinations. In: Guilleminault C, Dement WC, Passouant P, editors. Narcolepsy. New York: Spectrum; 1976. p. 145–60.

Rondot P, de Recondo J, Coignet A, Ziegler M. Mental disorders in Parkinson's disease after treatment with L-DOPA. Adv Neurol 1984; 40: 259–69.

Saint-Cyr JA, Taylor AE, Lang AE. Neuropsychological and psychiatric side effects in the treatment of Parkinson's disease. [Review]. Neurology 1993; 43 (12 Suppl 6): S47–52.

Sanchez-Ramos JR, Ortoll R, Paulson GW. Visual hallucinations associated with Parkinson's disease. Arch Neurol 1996; 53: 1265–8.

Shergill SS, Walker Z, Le Katona C. A preliminary investigation of laterality in Parkinson's disease and susceptibility to psychosis [letter]. J Neurol Neurosurg Psychiatry 1998; 65: 610–11.

Shimomura T, Mori E, Yamashita H, Imamura T, Hirono N, Hashimoto M, et al. Cognitive loss in dementia with Lewy bodies and Alzheimer disease. Arch Neurol 1998; 55: 1547–52.

Souques MA. Rapport sur les syndromes parkinsoniens. Rev Neurol (Paris) 1921; 37: 534–73.

Tandberg E, Larsen JP, Aarsland D, Laake K, Cummings JL. Risk factors for depression in Parkinson disease. Arch Neurol 1997; 54: 625–30.

Tanner CM, Vogel C, Goetz CG, Klawans HL. Hallucinations in Parkinson's disease: a population study [abstract]. Ann Neurol 1983; 14: 136.

Teunisse RJ, Cruysberg JR, Hoefnagels WH, Verbeek AL, Zitman FG. Visual hallucinations in psychologically normal people: Charles Bonnet's syndrome. Lancet 1996; 347: 794–7.

Tulving E, Schacter DL. Priming and human memory systems. Science 1990; 247: 301–6.

Turner TH, Cookson JC, Wass JA, Drury PL, Price PA, Besser GM. Psychotic reactions during treatment of pituitary tumours with dopamine agonists. Br Med J 1984; 289: 1101–3.

Vander Borght T, Minoshima S, Giordani B, Foster NL, Frey KA, Berent S, et al. Cerebral metabolic differences in Parkinson's and Alzheimer's diseases matched for dementia severity. J Nucl Med 1997; 38: 797–802.

Vidailhet M, Bonnet AM, Belal S, Dubois B, Marle C, Agid Y. Ropinirole without levodopa in Parkinson's disease [letter]. Lancet 1990; 336: 316–7.

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