INTERNATIONAL JOURNAL OF GERIATRIC PSYCHIATRY
Int J Geriatr Psychiatry 2005; **20**: 668–673.
Published online in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/gps.1339

Frontal dysfunction contributes to the genesis of hallucinations in non-demented Parkinsonian patients

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SUMMARY

Background Hallucinations occur in patients with Parkinson's disease (PD) with reported prevalence ranging from 8% to 40%. Hallucinations are significantly associated with dementia in PD, but little is known about possible distinctive cognitive features of non-demented PD patients who develop hallucinations.

Objective The aim of the study was to assess selected cognitive abilities in non-demented PD patients with and without hallucinations in order to identify specific neuropsychological correlates of such phenomena.

Methods Forty-eight consecutive patients with PD and Mini Mental State Examination (MMSE) ≥ 23 were examined for the presence of hallucinations and assessed on standardized neuropsychological tasks for semantic and phonological fluency, verbal learning and logical abstract thinking; disease severity was staged according to Hoehn and Yahr scale.

Results Fourteen (29.2%) of 48 patients experienced hallucinations. There was no difference between hallucinators and non-hallucinators on demographic variables, disease severity and dose of any pharmacological treatment. Disease duration was significantly longer in hallucinator *vs* non-hallucinator patients ($p = 0.02$). Patients with hallucinations scored significantly lower than patients without hallucinations only on verbal learning—immediate recall task ($p = 0.0324$), and semantic and phonological fluency tasks ($p = 0.0005$ and $p = 0.0036$, respectively).

Conclusions Our results suggest that PD patients with hallucinations show reduced performance on tasks that explore executive functioning as compared with non-hallucinators. Therefore, executive dysfunction may be considered as a risk factor for the development of hallucinations in non-demented PD patients. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS — Hallucinations; Parkinson's disease; Executive functions; Frontal lobe

Hallucinations occur in patients with Parkinson's disease (PD) with a prevalence ranging from 8% to 40% (Barnes and David, 2001) and are associated with major behavioral and functional problems and higher mortality (Holroyd *et al.*, 2001). Although hallucinations are considered as a side-effect of antiparkinsonian treatment, most studies failed to show relevant differences in drug treatment between PD patients with and without hallucinations (Sanchez-Ramos *et al.*, 1996; Graham *et al.*, 1997; Aarsland *et al.*, 1999; Goetz, 1999; Holroyd *et al.*, 2001). Other factors commonly associated with hallucinations are greater age, longer disease duration, sleep disorders and depression (Comella *et al.*, 1993; Sanchez-Ramos *et al.*, 1996; Fenelon *et al.*, 2000; Barnes and David, 2001). Previous clinical studies have shown that the presence of global cognitive impairment is associated with a higher risk of developing hallucinations (Meco *et al.*, 1990; Sanchez-Ramos *et al.*, 1996; Graham *et al.*, 1997). It has been proposed that cognitive impairment reflects a general degradation in information processing abilities, predisposing to hallucinations (Barnes and David, 2001). However, the specific role of cognitive dysfunction in the genesis of hallucinations in PD patients has been poorly investigated.

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Received 26 July 2004
Accepted 2 February 2005

Our aim was to verify whether specific cognitive patterns may characterise PD patients who develop hallucinations; for this purposes we compared non-demented PD patients with and without hallucinations on several neuropsychological tasks tapping controlled verbal production, verbal learning and abstract logical thinking.

PATIENTS AND METHODS

A series of consecutive outpatients seen at the University of Naples movement disorder unit and diagnosed with Parkinson's disease according to Parkinson's Disease Society Brain Bank criteria (Gibb and Lees, 1988) were examined in this study. In order to exclude patients with possible cognitive deterioration and dementia, we enrolled subjects who obtained a normal score on Mini Mental State Examination (MMSE; Folstein *et al.*, 1975), a short screening questionnaire, administered according to Italian norms (Measso *et al.*, 1993); an age- and education-adjusted score equal to or greater than 23.8 is considered normal. As major depression is a known confounding factor for neuropsychological disorders, patients meeting DSM-IV criteria for current major depression were excluded. Moreover, we excluded patients who presented relevant depressive signs and symptoms as expressed by a score higher than 16 at the 17-item Hamilton Rating Scale for Depression (Hamilton, 1960). Last, patients with clinically significant or unstable medical condition including serious cardiovascular, pulmonary or hepatic disease were excluded from the study.

Forty-eight patients met these criteria and gave their consent to participate to the study. Age, education, duration of illness and medication were recorded and illness severity was staged according to Hoehn and Yahr scale (Hoehn and Yahr, 1967). All patients were treated with levodopa alone or a combination of levodopa and a dopamine-agonist (pramipexole, ropinirole or pergolide). In order to take into account the amount of all dopaminergic drugs taken, we calculated a levodopa-equivalent dose for each patient. None of the patients was treated with anticholinergic medications.

All selected patients underwent a specific questionnaire devised to investigate present or past occurrence of visual or auditory hallucinations, content, frequency and duration of these phenomena, and patients' affective and emotional reaction in response to their hallucinations.

After completing MMSE, patients underwent the neuropsychological evaluation aimed to assess selected cognitive abilities by means of tests standardized on an Italian sample. The neuropsychological assessment battery comprised the following tests:

- Semantic (Spinnler and Tognoni, 1987) and phonological verbal fluency (Caltagirone *et al.*, 1979), two tests of controlled verbal production. The phonological fluency task required the production of words beginning with the letters F, A and S within a 60-sec period. The semantic fluency task required the production of words belonging to four semantic categories, each within 2 min. Both tests represent a measure of verbal attainment, thought to be sensitive to frontal lobe lesions.
- Rey auditory 15-word learning test (Caltagirone *et al.*, 1979), to assess verbal memory. This test is a measure of verbal learning and memory in which a list of 15 items is presented five times, each presentation followed by free recall (immediate free recall). Following a 15-min delay, delayed free recall is tested. Two measures were computed: the total number of words recalled after the five consecutive presentations (range of performance: 0–75) and the number of words recalled after a 15-min delay (range of performance: 0–15). These indexes are representative of the learning and recall processes, respectively; moreover, from single patients' scores, it is possible to calculate an index of learning efficiency (the difference between the average score of the pooled 4th and 5th recalls and that of the pooled 1st and 2nd recalls, expressed as a fraction of the former score) and an index of forgetting rate (the difference between the average score of the pooled 4th and 5th recalls and the score achieved at the delayed recall, expressed as a fraction of the former score; see Antonelli-Incalzi *et al.*, 2003).
- Raven's 47 Coloured Progressive Matrices (RCPM, Caltagirone *et al.*, 1979). RCPM consist of a set of abstract visual patterns that subjects have to complete by choosing an item among six alternatives. This test is considered to evaluate abstract non-verbal reasoning, but it is clearly influenced by visuo-perceptual factors.

The neuropsychological battery was administered by a trained psychologist, and completed in a single session lasting one to two hours.

Statistical analysis

Demographic, clinical and neuropsychological features of patients with and without hallucinations were compared by *t*-tests for independent samples or by

chi-square analysis, as appropriate. A multivariate analysis of covariance was performed on the neuropsychological scores to verify the possible differences between the two groups independently of demographic and clinical significant divergences.

RESULTS

Fourteen (29.2%) of the 48 patients enrolled in the study had experienced hallucinatory phenomena. Patients with and without hallucinations did not differ for sex, age, Hoehn and Yahr clinical stage, and levodopa-equivalent daily dose. There were no differences in the proportion of patients treated with dopamine-agonist (9/14, 64.2%, in patients with hallucinations *vs* 11/34, 67.6%, in patients without hallucinations) nor in the type of dopamine-agonist between patients with and without hallucinations. Patients with hallucinations showed significantly higher level of formal education and longer disease duration than patients without hallucinations (Table 1).

As regards phenomenology, hallucinations occurred only in the visual modality in 9/14 patients (64.3%), and had a secondary auditory component in three patients (21.4%); two patients (14.3%) experienced pure auditory hallucinations. Visual hallucinations consisted in fully formed images of people and/or animals in nine patients, and of objects or shades in three patients.

Hallucinations appeared after a mean disease duration of 5.3 years. Six patients (42.8%) experienced hallucinations several times a week, six (42.8%) several times a month, and two (14.4%) reported hallucinations only once or twice in a month. Hallucinations occurred in the morning in 14.3% of the patients, in the afternoon in 7.1%, in the evening or night in 28.6% of patients; in the remaining seven patients hallucinations occurred at any time through the day. Hallucinations lasted a few seconds in 71.3% of patients and a few minutes in the remaining 28.7%. Indifference was reported in response to hallucinations in most patients (57.1%), fear was reported in five patients (35.7%). Neuropsychological results are reported in Table 2. There were no differences in MMSE score ($p = 0.521$), delayed free recall ($p = 0.477$) and RCPM score ($p = 0.153$) between patients with and without hallucinations. Patients with hallucinations showed poorer performance on phonological fluency ($p = 0.0036$), semantic fluency ($p = 0.0005$) and immediate free recall ($p = 0.0324$). There was a trend toward a lower verbal learning efficiency in patients with hallucinations than in patients without hallucination (learning efficiency index: 0.25 ± 0.31 and 0.39 ± 0.16, respectively; $t = -0.1973$, df = 45, $p = 0.055$), while forgetting rate did not differ in the two groups (forgetting index: 0.41 ± 0.27 and 0.48 ± 0.21, respectively; $t = -0.994$, df = 45, $p = 0.325$).

Multivariate analysis performed on the six neuropsychological variables (MMSE score, immediate and delayed recall, RCPM score, semantic and phonemic fluency), with education and duration of disease as covariates, showed that the two groups (patients with and without hallucinations) did not differ from each other (Wilks' lambda = 1,228, df = 6,33, $p = 0.317$). The differences between the two groups on Rey immediate recall ($p = 0.0181$), and on semantic ($p = 0.0004$) and phonemic fluency ($p = 0.0033$) remained significant.

It is worth mentioning that, although we excluded from our sample patients affected by possible cognitive deterioration on the basis of pathological MMSE scores, a small proportion of patients with or without hallucinations achieved pathological scores on select neuropsychological tasks with respect to Italian normative data. In particular, among patients with hallucinations 4/14 scored lower than normal controls on the phonemic fluency task, 1/14 on the semantic fluency task, and 6/14 on the Rey immediate recall. Among patients without hallucinations, none achieved a pathological score on the phonemic fluency task, while 1/34 and 6/34 patients scored low on the semantic fluency and the Rey immediate recall, respectively. Only the proportion of pathological

Table 1. Demographic and clinical features of PD patients with and without hallucinations [Mean (SD)]

	Hallucinators ($n = 14$)	Non-hallucinators ($n = 34$)	χ^2/t value	*P*
Sex (M/F)	9/5	20/14	0.124	0.725
Age (y)	67.36 (10.73)	66.85 (9.17)	0.165	0.87
Education (y)	12.71 (4.05)	8.53 (4.38)	3.07	**0.0036**
Disease duration (y)	10.38 (7.29)	6.29 (4.2)	2.407	**0.0202**
Hoehn & Yahr stage	2.77 (0.63)	2.47 (0.78)	1.234	0.22
Levodopa equivalent dose (mg/day)	450 (263.1)	437.9 (249.2)	0.150	0.88

Significant *p* values are highlighted in bold.

Table 2. Cognitive comparisons of hallucinators vs non hallucinators [Mean (SD)]

	Hallucinators ($n = 14$)	Non-hallucinators ($n = 34$)	Normal cut-off*	*t*-value	*P*
MMSE	26.56 (2.15)	27 (2.13)	23.8	−0.647	0.521
RCPM	21.46 (6.09)	24.38 (6.19)	18.96	−1.453	0.153
Phonological fluency	23.81 (8.31)	31.57 (7.49)	17.35	−3.076	**0.0036**
Semantic fluency	10.37 (3.61)	14.9 (3.69)	7.00	−3.789	**0.0005**
Immediate free recall	29.93 (8.51)	35.51 (7.45)	28.53	−2.207	**0.0324**
Delayed free recall	6.82 (2.49)	7.49 (2.96)	4.69	−0.716	0.477

For each test, cut-off values are intended for age-and education-adjusted scores, as reported in the respective Italian normative studies (see text for references).
Significant *p* values are highlighted in bold.

scores on the phonemic fluency test was significantly different in the two groups of patients (chi square = 10.6, df = 1, $p = 0.001$).

DISCUSSION

In this sample of consecutive non-demented patients with strictly defined PD, prevalence of hallucinations was 29.2%. This is consistent with previous prevalence studies (Tanner *et al.*, 1983; Inzelberg *et al.*, 1998; Holroyd *et al.*, 2001) and emphasizes the importance of hallucinations as clinical issue for patients with PD. In agreement with previous studies (Sanchez-Ramos *et al.*, 1993; Graham *et al.*, 1997), hallucinations were mainly experienced in the visual modality, although an auditory component was present in 35.7% of patients experiencing hallucinations. Other phenomenological findings from this study also concur with previous investigations, with respect to content, temporal features and insight for hallucinations (Graham *et al.*, 1997; Fenelon *et al.*, 2000; Holroyd *et al.*, 2001; Barnes and David, 2001).

It has been reported that visual hallucinations may be correlated with different kinds of sleep disorders in PD (Kulisevsky and Roldan, 2004). We did not evaluate such phenomena systematically, because of the lack of an Italian version of available scales (e.g. Chaudhuri and Martinez-Martin, 2004). However, in our sample standard clinical and anamnestic evaluation revealed similar frequency of sleep disorders in hallucinators (62%) and non-hallucinators PD patients (58%).

In the present study, disease duration emerged as a relevant variable associated with hallucinations. This finding is consistent with previous studies, where the illness duration seems to be a crucial factor to the development of hallucinations in PD (Sanchez-Ramos *et al.*, 1996; Graham *et al.*, 1997; Fenelon *et al.*, 2000). The hallucinators did not differ from the non-hallucinators with respect to age, disease severity, and daily dopaminergic medication. The lack of relationship between the dose of dopaminergic drugs and hallucinations is in line with results of previous studies (Sanchez-Ramos *et al.*, 1996; Graham *et al.*, 1997; Aarsland *et al.*, 1999; Holroyd *et al.*, 2001), and suggests that hallucinations are not a simple dopaminergic adverse event but a symptom related to the disease itself, although facilitated or triggered by medication.

Since cognitive functions in non-demented patients with and without hallucinations have been poorly investigated, our main aim was to identify specific neuropsychological deficits related to such phenomena. We found that fluency tasks and immediate free recall in verbal learning are impaired in hallucinators as compared with non-hallucinators. Phonological and semantic fluency are well-known frontal sensitive tasks, and have been frequently found impaired in PD patients (Bouquet *et al.*, 2003). Both phonological and semantic fluency decline over the disease course and this finding has been interpreted as an index of the progressive deterioration of executive functions in non-demented PD patients (Azuma *et al.*, 2003). Free recall tasks are a measure of verbal learning that requires active organization of the to-be-remembered material (Taylor *et al.*, 1986; Mohr *et al.*, 1990), and have been widely used in Parkinson's disease (Ivory *et al.*, 1999). Although data from literature were not always consistent, non-demented PD patients may show memory deficits attributable to frontal lobe dysfunction (Ivory *et al.*, 1999). Therefore, reduced fluency, verbal learning and learning efficiency in our patients with hallucinations (in presence of normal delayed recall) may be ascribed to a relative dysfunction of controlling and monitoring (executive) functions subtended by pre-frontal cortex. Executive dysfunction is a common neuropsychological finding in PD (Taylor *et al.*, 1990; Pillon *et al.*, 1991; Brown *et al.*, 1997; Owen *et al.*, 1998), even in untreated patients at early stages of disease (Dujardin *et al.*, 1999), but

its possible contribution to the development of hallucinations has never been discussed in the patients.

Recently, Barnes *et al.* (2003) compared 17 PD patients with hallucinatmions with a group of 20 PD patients without hallucinations on a range of tasks exploring visuospatial processing, imagery and visual recognition abilities. Barnes *et al.* (2003) found that hallucinators scored lower than non-hallucinators on several tests exploring visual perception and recognition and also showed lower scores on a source monitoring subtest, in which the patients had to decide whether a certain stimulus had been presented as a word or as a picture. The authors argued that defects in visual processing and in source monitoring contribute to the development of hallucinations, which may be interpreted as resulting from a defect in disentangling internal representations and real events (Bentall and Slade, 1991; Johnson, 1991). Source-monitoring deficits have been associated with the temporal and frontal areas (Henkel *et al.*, 1998).

Although partially conflicting with Barnes *et al.*'s (2003) study, in which no difference was observed on a fluency test, our findings would suggest that relative frontal dysfunction, as evidenced by simple tasks widely used in clinical setting, may play a critical role in the genesis of hallucinations. As verbal fluency performance declines with PD progression (Azuma *et al.*, 2003), it is worth underlining that multivariate analysis showed that reduced verbal fluency and immediate recall correlated with the presence of hallucinations independently from disease duration. In agreement with Barnes *et al.* (2003), it is possible to speculate that the cognitive mechanism through which frontal dysfunction is related to hallucinations is mainly represented by a failure in source-monitoring.

In conclusion, the present study provides new insight into the pathophysiology of hallucinations in non-demented PD patients, and suggests that frontal dysfunction may have a critical role in the production of hallucinations. Further investigations are required to verify the usefulness of simple executive tasks in identifying PD patients at risk for the development of hallucinations.

ACKNOWLEDGEMENT

The authors thank Valentina Ravallese for her contribution in collecting patients' data.

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