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Cognitive correlates of visual hallucinations in non-demented Parkinson's disease patients

D.H. Hepp [a,b,*], C.C. da Hora [a], T. Koene [c], B.M. Uitdehaag [a,d], O.A. van den Heuvel [b,e], M. Klein [c], W.D. van de Berg [b], H.W. Berendse [a], E.M. Foncke [a]

[a] Department of Neurology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands
[b] Department of Anatomy and Neurosciences, Section Functional Neuroanatomy, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands
[c] Department of Medical Psychology, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands
[d] Department of Epidemiology and Biostatistics, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands
[e] Department of Psychiatry, Neuroscience Campus Amsterdam, VU University Medical Center, Amsterdam, The Netherlands

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ABSTRACT

Background: Visual hallucinations (VH) in Parkinson's disease (PD) are associated with PD dementia and have been related to cognitive impairments in non-demented PD patients. Reports on the specific cognitive domains affected are conflicting. The aim of the present study was to investigate the presence of specific cognitive impairments in non-demented PD patients with VH, compared to those without VH.
Methods: We compared the clinical characteristics and neuropsychological test scores of 31 non-demented PD patients with VH with those of 31 PD patients without VH that were carefully matched for sex, age, disease duration and educational level. Several non-motor symptoms, including depression, anxiety and sleep disturbances, were also taken into account, as these may influence cognitive performance.
Results: The PD with VH group performed significantly worse on the Trail Making Test part A ($p = 0.01$) and the Rey Auditory Verbal Learning Test, immediate recall ($p = 0.01$). In addition, PD patients with VH were more anxious, more depressed and reported more sleep disturbances. Verbal learning scores were not associated with levels of anxiety, depression or sleep disruption, whereas worse Trail Making Test A performance was associated with concomitant sleep disturbances.
Conclusions: In non-demented PD patients, the presence of VH is associated with a cognitive profile characterized by impairments in verbal learning and probably attention. Since these cognitive functions are believed to be non-dopaminergic mediated functions, the present results support the hypothesis that multiple neurotransmitter systems, other than dopamine, contribute to the pathophysiology of VH in PD.

1. Background

Visual hallucinations (VH) occur in one quarter to one third of patients with Parkinson's disease (PD), with life time prevalence estimates of up to 74 percent [1,2]. VH constitute a major source of distress to patients and caregivers and are the strongest independent predictor of nursing home placement in PD patients [3]. Development of more effective treatment strategies for VH is hindered by an incomplete knowledge of the pathophysiology of VH in PD. For decades, VH were considered a mere side-effect of dopaminergic treatment. However, there is little evidence for a strong relationship between levodopa dose and the occurrence of VH. Moreover, high-dose intravenous levodopa infusions failed to provoke VH in PD patients [1]. Recent studies propose integrative models to explain VH in PD in which, besides dopaminergic stimulation, also alterations of sleep-wake and dream regulation, impaired attentional focus and dysfunction of visual pathways, are suggested to contribute to the etiology of VH in PD [4–8]. In these models, involvement of non-dopaminergic, including cholinergic, neurotransmitter systems has been implicated [4,5].

Clinically, the most consistent correlate of VH in PD is cognitive impairment. Fenelon et al. demonstrated that severe cognitive impairment, in addition to daytime somnolence and disease duration, is associated with the occurrence of VH [9]. In an 8-year prospective study, the presence of VH at baseline proved a significant predictor of PD dementia [10]. Furthermore, even in

* Corresponding author. Department of Neurology, VU University Medical Center, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands. Tel.: +31 20 444 6179; fax: +31 20 444 8054.
E-mail address: d.hepp@vumc.nl (D.H. Hepp).

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non-demented PD patients suffering from VH, cognitive impairments have been described [11–14]. Identification of specific cognitive dysfunctions in non-demented PD patients with VH might give more insight into the pathophysiological mechanisms underlying VH, since Kehagia et al. recently suggested that distinct neuroanatomical regions and neurotransmitter systems are involved in the disturbances of specific cognitive functions in PD. They distinguish a fronto-striatal, dopaminergic dependent circuit from an extra-striatal circuit, mainly influenced by cholinergic changes. The former is involved in executive functions such as planning and concept formation, while the latter plays a role in mnemonic features of cognition, including visual recognition memory, associative learning and attention [15].

Several previous studies analyzed patterns of cognitive impairment in non-demented PD patients with VH, but results have so far been rather variable. Executive dysfunction [11,12,14] but also disturbances in visuoperception [8,13] as well as in verbal learning and memory [12–14] have been reported. The variability in cognitive impairments might be partly explained by differences in disease duration, disease severity or medication use between patient groups in these studies [11–14]. In the present study we investigated the presence of specific cognitive impairments in non-demented PD patients with VH (PD + VH), in comparison to PD patients without VH (PD − VH). To overcome previous pitfalls, we carefully matched the patient groups for sex, age, disease duration and educational level. In addition, we evaluated the presence of specific comorbid non-motor symptoms, in particular depression, anxiety and sleep disturbances, as these may influence cognitive performance.

2. Material and methods

2.1. Subjects

Data were obtained retrospectively from patients who were referred to the outpatient clinic for Movement Disorders at the VU University Medical Center, Amsterdam, the Netherlands. All patients gave written informed consent to store their medical information in a database and to use these data for scientific research, which was approved by the local Medical Ethical Committee.

All patients were diagnosed with idiopathic PD by a movement disorder specialist (HB or EF) according to the UK PD Brain Bank criteria [16]. Patients with evidence of global dementia (MMSE score ≤ 23 and/or a diagnosis of dementia based upon extensive neuropsychological evaluation) or a history of severe visual impairment were excluded from this study. Of 296 non-demented PD patients, 273 patients and their caregivers were routinely questioned on the presence of VH using the SCOPA PC; a reliable, valid and easy-to-administer questionnaire for psychotic complications in PD [17]. Thirty-five patients (35/273; 13%) had experienced VH within the previous month. Almost all non-demented PD patients with VH ($n = 31$) had extensive neuropsychological examinations as part of the diagnostic work-up and were included in this study. For every hallucinating non-demented PD patient a search was performed among the non-demented patients without VH to match for sex, age, disease duration and educational level. Only patients with SCOPA PC assessment and extensive neuropsychological examination at the same clinical visit were included.

The level of education was classified using the system of Verhage [18], ranging from 1 (elementary school not finished) to 7 (university). Clinical assessment of patients included severity of motor symptoms (Unified Parkinson Disease Rating Scale, part III) and disease stage (Hoehn and Yahr stage). Self-reported inventories, the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI), were used to assess severity of depressive symptoms and anxiety, respectively. SCOPA Sleep questionnaires [19] were administered to record sleep disturbances. In addition, the levodopa equivalent daily dose (LEDD) was calculated for each patient as described elsewhere [20] and the use of other relevant medication (i.e. amantadine, neuroleptics, anticholinergics, antidepressants and benzodiazepines) was registered.

2.2. Neuropsychological assessment

Neuropsychological examination comprised the following five cognitive domains: attention, memory, visuospatial function, language and executive function. The forward condition of the Digit Span Test (DS) [21] and part A of the Trail Making Test (TMT_A, score expresses the number of seconds needed) were used to assess attention. In keeping with previous studies, we calculated a difference score between part A and B of the TMT (TMT_{B-A}) to explore the specific component of attentional set shifting [7]. For verbal learning, delayed recall and recognition a modified version of the Rey Auditory Verbal Learning Test was used (RAVLT immediate recall: 5 trials of 15 words, range 0–75; RAVLT delayed recall: 1 trial, range 0–15; RAVLT recognition, 1 trial: range 0–30, RAVLT false recognition, range 0–30) [22]. Mere automatic memory registration was assessed with the Visual Association Test (VAT, 2 trials of 12 cards, range 0–24) [23].

The Rey Complex figure immediate drawing and delayed recall [24] were performed to measure visuoconstruction and visual memory. Language performance was measured with a short version A of the Boston Naming Test. Categorical fluency and semantic fluency were tested by asking the subject to produce as many animals and as many words starting with the letters D, A and T as possible within a time span of 60 s. The backward condition of the DS was used to assess executive function and is reported as index to correct for attention. Executive function was further tested using the Stroop Color word interference test [25] (scores shown are scores for part III divided by the scores for part II, to correct for speed).

2.3. Data analysis

All statistical analyses were performed with IBM Statistical Package of the Social Sciences software version 20.0 (SPSS, Chicago, Il, USA). Gender distribution between patient groups (PD + VH and PD − VH) was compared with the Fisher exact test. For univariate group comparisons of clinical and cognitive variables an independent *t*-test was performed for normally distributed data (age and UPDRS III) and the Mann–Whitney *U*-test for non-normally distributed data. Because of the explorative character of the study we chose not to correct for multiple comparisons. The Spearman correlation coefficient evaluated correlations between different variables. Based on the strength of the association between different variables and the dichotomous outcome (presence or absence of VH) a multivariate analysis was performed using binary logistic regression. Statistical significance was set at 0.05.

3. Results

The prevalence of VH in our outpatient clinic population of non-demented PD patients was 13%. As expected, there were no statistically significant group differences in sex, age, disease duration or educational level between PD + VH and PD − VH (see Table 1). In addition, disease stage (H&Y), severity of motor symptoms (UPDRS III), LEDD and the use of other relevant medication, including use of antidepressants and benzodiazepines (data not shown), were comparable between groups. Table 2 shows the scores on all neuropsychological tests ordered by cognitive domain. PD + VH, compared with PD − VH, were significantly slower on the TMT_A ($p = 0.01$) and there was a trend for a lower TMT difference score in PD + VH ($p = 0.07$). Furthermore, PD + VH performed significantly worse on the modified RAVLT immediate recall ($p = 0.01$). Performance speed on TMT_A correlated negatively with accuracy on the

Table 1
Demographic and clinical characteristics of PD patients with and without VH (Mean ± SD).

	PD + VH	PD − VH	*p*
N	31	31	
Men nr. (%)	18 (58)	20 (65)	0.80
Age years	66 ± 11	65 ± 11	0.53
Disease duration years	7 ± 5	8 ± 5	0.48
MMSE	27 ± 2	28 ± 2	0.36
Verhage education score	5.2 ± 1.3	4.9 ± 1.7	0.62
UPDRS III	32 ± 15	26 ± 11	0.11
H&Y median (range)	2.5 (1–4)	2.5 (1–4)	0.57
BAI	42 ± 11	35 ± 11	<**0.01***
BDI	17 ± 9	12 ± 10	**0.02***
SCOPA Sleep	29 ± 10	21 ± 7	<**0.01***
LEDD mg	508 ± 518	602 ± 703	0.64
Treatment with DA nr. patients	12	11	
Treatment with amantadine nr. patients	2	4	
Treatment with neuroleptics nr. patients	3	0	
Treatment with anticholinergics nr. patients	3	3	

Abbreviations: MMSE = Mini-Mental State Examination, UPDRS III = Unified Parkinson's Disease Rating Scale part III, H&Y = Hoehn and Yahr stage, BAI = Beck Anxiety Inventory, BDI = Beck Depression Inventory, SCOPA Sleep = Scales for Outcomes in Parkinson's disease-Sleep Scale, LEDD = Levodopa Equivalent Daily Dose, DA = Dopamine Agonist.
*Difference is statistically significant ($p < 0.05$).

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