eNeurologicalSci 4 (2016) 25–29

Contents lists available at ScienceDirect

eNeurologicalSci

journal homepage: http://ees.elsevier.com/ensci/

Fatigue is associated with the onset of hallucinations in patients with Parkinson's disease: A 3-year prospective study

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ARTICLE INFO

Article history:
Received 18 February 2016
Accepted 9 April 2016
Available online 16 April 2016

Keywords:
Parkinson
Hallucination
Predictable factor
Risk factor
Fatigue

ABSTRACT

Hallucinations remain problematic in Parkinson's disease (PD). Various factors have been studied, and many previous studies identified risk factors for hallucinations, such as sleep disorders. At the same time, fatigue is a common symptom in Parkinson's disease, and any factors associated with fatigue in PD have been reported. Factors associated with fatigue in PD are likely to be similar to risk factors for hallucinations. However, fatigue has been not been reported to be a risk factor for hallucinations in previous studies. We prospectively studied non-hallucinators with PD during 3 years to identify factors associated with the onset of hallucinations, including fatigue. We initially screened 100 consecutive patients and registered 78 patients with PD. During 3 years of follow-up, 31 patients newly presented with visual hallucinations. A total of 18 variables were evaluated by logistic regression analysis. Brief Fatigue Inventory (BFI) (OR = 1.027, p = 0.045, 95% CI = 1.001–1.053) was related to first-onset hallucinations on multivariate logistic regression analysis. The present study is the first to demonstrate an association of fatigue with the onset of hallucinations. Fatigue, especially mental fatigue, can be a risk factor for future hallucinations.

1. Introduction

Hallucinations remain problematic in Parkinson's disease (PD) because they negatively affect the quality of life of not only the patients, but also the caregivers. We often encounter patients with new-onset hallucinations that progress to uncontrolled delirium. Knowledge about predictable risk factors for first-onset hallucinations is thus very important. Various factors have been studied, and many previous studies identified risk factors for hallucinations, such as older age, female gender, prolonged disease duration, depression, daytime somnolence, insomnia, excessive daytime sleepiness, cognitive impairment, severity of motor symptoms, motor complications, autonomic dysfunction, and medication dosage [4,11,14,17,42]. In particular, sleep disorders, including rapid eye movement (REM)-sleep behavioral disorder, dream-enacting behavior, and nightmares, are known to an important risk factor for hallucinations [4,11,14,17]. At the same time, fatigue is a common symptom in Parkinson's disease (PD), ranging in prevalence from 37% to 56% [6]. Many factors associated with fatigue in PD have been reported, such as PD duration, female gender, depression, sleep disturbance, excessive daytime sleepiness, REM behavioral disorder, motor symptoms, autonomic dysfunction, apathy, and dopaminergic treatment [2,5,6,32,38,40]. Now, the presence or severity of fatigue is recognized to be significantly associated with both motor and non-motor symptoms in PD [37]. Factors associated with fatigue in PD are likely to be similar to risk factors for hallucinations. To our knowledge, however, fatigue has been not been reported to be a risk factor for hallucinations in previous studies [4,11,14,17,42]. We prospectively studied non-hallucinators with PD during 3 years to identify factors associated with the onset of hallucinations, including fatigue and sleep disorders.

2. Material and methods

2.1. Participants and initial assessments

We initially screened 100 consecutive patients who fulfilled the UK Parkinson's Disease Society Brain Bank criteria [22]. In accordance with our recently reported methods [26,27], we first had the patients complete diary questionnaires for 4 weeks (Supplemental material 1) to exclude patients who had hallucinations or who had dementia or higher brain dysfunction that would preclude following our instructions. The clinical diary included a total of 10 questions and inquired about hallucinations (item 9), vivid nightmares (items 1 and 2), dream-enactment behavior (items 3, 4, 5, and 7), and sleep fragments associated with vivid dreams (item 8). Items 3, 5, 7, and 9 were asked to both the patients and their bed partners. The patients wrote their responses to the questions after awakening in the morning. If a patient had drunk alcohol the previous night (item 10), we did not use their

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http://dx.doi.org/10.1016/j.ensci.2016.04.001

responses for last night. If they did not remember any dream or the experienced dreams were not judged to be nightmares, we did not use the responses associated with such dreams. Patients who responded that they had hallucinations (item 9) were excluded. Patients who were given quetiapine, clozapine, rivastigmine, donepezil, galanthamine, yokukansan, or neuroleptic medications were excluded. Patients who had received deep brain stimulation surgery or a previous diagnosis of schizophrenia, as well as patients who had a history of hallucinations were also excluded. The severity of PD was graded according to the scores on the Unified Parkinson's Disease Rating Scale (UPDRS) [13]. Cognition function was assessed with the Mini-Mental Status Examination (MMSE). The Brief Fatigue Inventory (BFI) included the evaluation of the severity of fatigue itself at the present time and during the past 24 h and of the impairment of 6 activities of daily living (general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life), and the degree of each activity was rated from "no fatigue" and "does not interfere" (0 points) to "bad" and "completely interferes" (10 points), respectively [30]. The Zung Self-Rating Depression Scale (SDS) was used to evaluate depression [43]. SDS is widely used as a self-administered psychological test, and a high score indicates severer depression. Several studies have used SDS to evaluate depression in PD [25]. The Zung Self-Rating anxiety scale and Parkinson's Disease Sleep Scale (PDSS) [8] have also been used. PDSS items were grouped according to domain: sleep quality (items 1–3), nocturnal motor symptoms (items 9–13), and daytime somnolence (items 14 and 15) [34,39]. The daily dose of antiparkinsonian agents was converted into the equivalent dose of levodopa as follows: 100 mg standard levodopa = 140 mg controlled release levodopa = 10 mg, bromocriptine = 1 mg pergolide = 1.5 mg cabergoline = 5 mg ropinirole = 1 mg pramipexole = 10 mg selegiline [31,36]. No patient received rotigotine.

2.2. Follow-up assessments

From among the 100 patients, we registered 78 patients with PD (Fig. 1). In accordance with our previously described methods [26,27], the interviewer personally interviewed the patients once every 1 to 3 months to inquire about the presence or absence and the frequency of hallucinations in the visual, auditory, tactile, and olfactory domains, and we promptly obtained responses from all patients. The interviewer also inquired whether the hallucinations were with or without retained insight, threatening or not, and with or without delusions or delirium, and whether the patients or their caregivers suffered from the hallucinations. These questions were also asked to the patients' caregivers. If discordant responses were obtained, the interviewer used best judgment. During 3 years of follow-up, we excluded patients who showed evidence of epilepsy, stroke, transient ischemic attacks or who were admitted to the hospital because of physical problems such as cardiac failure or pulmonary infection or who had undergone surgical intervention. In addition, no patient who newly experienced hallucinations during the follow-up period had mental impairment, impaired consciousness, dementia, or impaired higher brain dysfunction such as

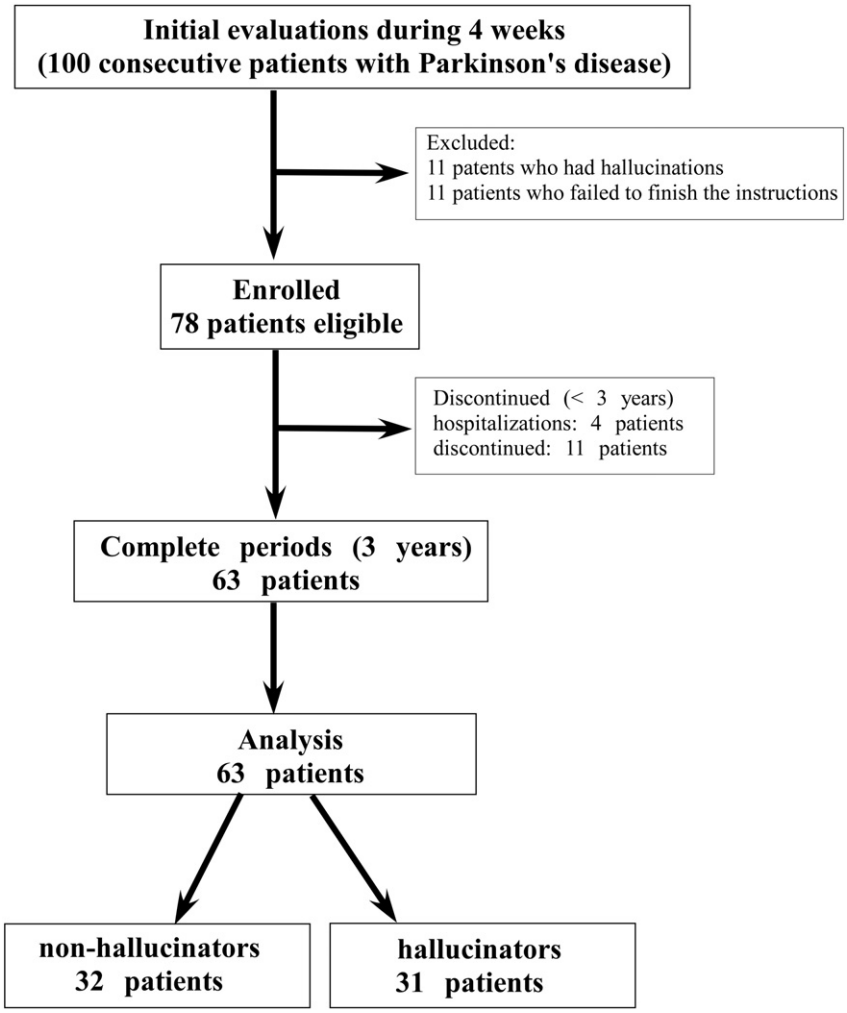

Fig. 1. Selection procedure for analyzing patients.

inattention or agnosia, which would have precluded following our instructions. The end point was defined as the presence of hallucinations. If a patient with first-onset hallucinations discontinued the study because of physical problems, the patient was included in the subsequent analysis. The study was discontinued in five patients with first-onset hallucinations (death in 2 and severe compression spinal fracture in 1). A total of 15 patients were excluded, and the remaining 63 patients were included in data analysis.

2.3. Statistical analysis

The 63 patients were divided to two groups: patients with hallucinations and those without hallucinations. Variables with a normal distribution are presented as the means ± SD, and variables with an asymmetrical distribution are presented as medians and the interquartile range (IQR). Variables that were not normally distributed were transformed to natural logarithms or categorical quartile groups. Differences in variables between patients with and those without first-onset hallucinations were evaluated by the Mann–Whitney test. A total of 18 variables were evaluated: variables were categorized as (1) age, (2) sex, (3) log-transformed disease duration, (4) log-transformed levodopa equivalent dose, (5) Hoehn–Yahr stage, (6) total UPDRS score, (7) UPDRS part III score, (8) motor complications (absent = 0, present [defined as an increased score on UPDRS part IV] = 1), (9) MMSE < 26, (10) SDS ≧ 50 [43], (11) Zung Self-Rating anxiety score ≧ 50 [16], (12) BFI, (13) log-transformed sum score of items on PDSS (excluding items 6 and 7, associated with dreams and hallucinations, respectively, which were rated from the direction of good to bad sleep), (14) sleep quality on PDSS, (15) log-transformed nocturnal motor symptoms on PDSS, (16) daytime somnolence on PDSS, (17) nightmares (absent = 0, present = 1), and (18) dream-enacting behavior (absent = 0, present = 1). Variables that were significantly related to the first-onset hallucinations on univariate logistic regression analysis ($p < 0.05$) were entered into multivariate logistic regression analysis using forced entry. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Correlations of significant independent variables on logistic regression analysis were evaluated by Spearman's rank correlation test. SPSS software (Version 18) was used for statistical analysis.

3. Results

A total of 31 patients newly presented with visual hallucinations, and six patients had both visual and auditory hallucinations. Hallucinations in eight patients were unaccompanied by retained insight. Delusions or delirium developed in four of the eight patients, and the three of these patients started to receive neuroleptic drugs. Nine patients had threatening hallucinations. At the final follow-up, eight patients or their caregivers suffered from hallucinations.

The log-transformed levodopa equivalent dose ($p = 0.034$), total UPDRS score ($p = 0.034$), and BFI ($p = 0.032$) differed significantly between patients with and those without first-onset hallucinations (Table 1 and Fig. 2). Univariate logistic regression analysis showed that BFI (OR = 1.029, $p = 0.023$, 95% CI = 1.004–1.055) and the total UPDRS score (OR = 1.031, $p = 0.043$, 95% CI = 1.001–1.073) were significantly related to first-onset hallucinations (Table 2). On multivariate logistic regression analysis, BFI (OR = 1.027, $p = 0.045$, 95% CI = 1.001–1.053) was related to first-onset hallucinations. There were no significant interactions between these predictive factors. Furthermore, when we additionally entered cognitive impairment as defined by a MMSE score of <26, which was reported to be a significant risk factor for hallucinations [4,11], into multivariate logistic regression analysis, the results similarly showed that BFI (OR = 1.026, $p = 0.048$, 95% CI = 1–1.053) was related to first-onset hallucinations.

Subitems on the BFI showed that the scores for general fatigue ($p = 0.02$), mood ($p = 0.042$), and relations with other people ($p = 0.021$) were significantly lower in patients with first-onset hallucinations than in those without hallucinations (Table 3). There was no difference between the two groups in the subscores for walking ability ($p = 0.184$), normal work including both work outside the home and dairy chores ($p = 0.07$), or enjoyment of life ($p = 0.129$).

4. Discussion

Our study uniquely showed that fatigue was a significantly associated with first-onset hallucinations. Many studies have attempted to identify factors associated with hallucinations, but the results have been inconsistent, and “fatigue” was not evaluated, except for one cross-sectional study of 81 patients with PD [37]. In contrast to our

Table 1
Basic characteristic of patients with Parkinson's disease who presented with the first-onset hallucination and those without hallucinations.

Variables	Total n = 63	Non-hallucinators n = 32	Hallucinators n = 31	p
Age, mean	69.8, 7.8	68.7, 9.1	71.0, 6.1	0.441
Male, n	26, 41.2	14, 43.7	12, 38.7	0.687
Disease duration, average (months)	50.73, 33.0	47.09, 32.0	54.48, 41.0	
Log-transformed, mean	3.57, 0.93	3.39, 1.02	3.74, 0.79	0.191
Total levodopa equivalent dose, average (mg/day)	229.77, 214.0	198.75, 146.0	261.80, 247.0	
Log-transformed, mean	4.68, 1.98	4.20, 2.30	5.17, 1.45	0.034*
Hoehn–Yahr stage	2.77, 0.63	2.62 0.70	2.93, 0.51	0.061
Total UPDRS score, mean	37.85, 15.66	33.84, 12.87	42, 17.34	0.034*
UPDRS part III, mean	23.90, 10.121	22.00, 9.16	25.87, 10.81	0.12
Motor complications, n	34, 53.9	16, 50.0	18, 58.0	0.706
MMSE < 26, n	10, 15.8	5, 15.6	5, 16.1	0.957
SDS ≧ 50, n	5, 7.9	1, 3.1	4, 12.9	0.154
Zung Self-rating anxiety score ≧ 50, n	7, 11.1	3, 9.3	4, 12.9	0.659
Brief Fatigue Inventory, mean	30.50, 21.76	24.25, 17.72	36.96, 23.87	0.032*
Total PDSS score, average	415.80, 373.0	377.62, 336.5	455.22, 386.0	
Log-transformed, mean	5.81, 0.70	5.71, 0.70	5.91, 0.69	0.383
Sleep quality on PDSS, IQR*	42.0 (20.6, 53.0)	42.0 (21.6, 47.6)	41.45 (18.6, 57.0)	1
Nocturnal motor symptoms on PDSS, average*	19.93, 14.6	16.85, 9.0	23.11, 20.4	
Log-transformed, mean	2.35, 1.39	2.13, 1.41	2.59, 1.36	0.157
Daytime somnolence on PDSS, IQR*	26.5 (5, 36.5)	24.5 (5, 37.0)	27.0 (11.0, 36.5)	1
Nightmare, n	21, 33.3	10, 31.2	11, 35.4	0.724
Dream enacting behavior, n	11, 17.4	4, 12.5	7, 22.5	0.296

UPDRS: new revised Unified Parkinson's Disease Rating Scale, PDSS: Parkinson's Disease Sleep Scale, MMSE: Mini-Mental Status Examination, SDS: Zung Self-Rating Depression Scale, n: number, data are reported as mean (SD), median (IQR: interquartile range), number (%) or average (median).
* Calculated the score from subscores on PDSS.

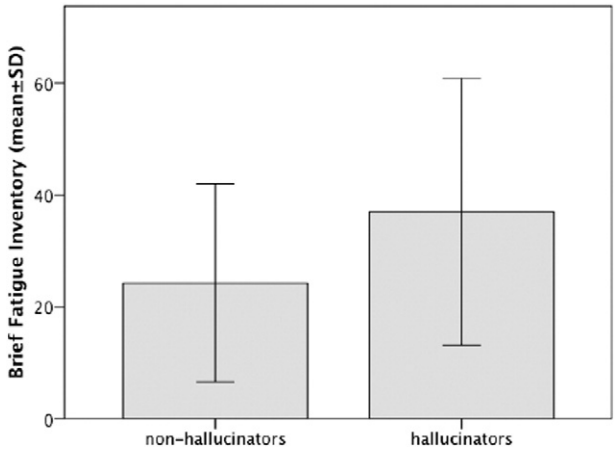

Fig. 2. Brief Fatigue Inventory between patients with Parkinson's disease who presented with the first-onset hallucination and those without hallucinations.

Table 3
Subitems of Brief Fatigue Inventory between patients with Parkinson's disease who presented with the first-onset hallucination and those without hallucinations.

	Non-hallucinators n = 32	Hallucinators n = 31	p
General fatigue (mean, median, range)	2.3, 2, 0–7	4.2, 4, 0–10	0.02**
Mood	2.1, 2, 0–5	3.6, 3, 0–10	0.042**
Walking ability	3.7, 3, 0–10	4.8, 5, 0–10	0.184
Normal work*	3.1, 3, 0–9	4.7, 5, 0–10	0.07
Relations with other people	1.8, 1, 0–8	3.7, 2, 0–9	0.021**
Enjoyment of life	2.4, 2, 0–8	3.7, 4, 0–10	0.129

* Includes both work outside the home and dairy chores.
** P < 0.05.

results, that study [37] did not find a significant association between fatigue and hallucinations despite the fact that the Parkinson's fatigue scale as well as the Fatigue Severity Scale were used to evaluate the degree of problems caused by fatigue. The reason for the different results might be attributed to the different means used to detect hallucinators: the previous study [37] was cross-sectional study, and the presence of hallucinations was evaluated on the basis of the Non-motor Symptoms Scale for PD; in contrast, our study prospectively identified first-onset hallucinations by repeated face-to-face interviews with the subjects. Also the presence of fatigue was methodically different, so the previous study used the cut-off value of both the Parkinson's fatigue scale and the Fatigue Severity Scale, and BFI in the present study used the rating scale.

Serotonin is closely associated with fatigue in chronic fatigue syndrome [10,41], and such patients showed widespread reduction of specific radioligand for serotonin 5-HT1A receptors on positron emission tomography (PET), particularly marked in the limbic areas including the hippocampus, amygdala, and insular and anterior cingulate [10]. Serotonin reuptake inhibitors are commonly used to treat chronic fatigue syndrome. In patients with PD, the postmortem brain tissue pathologically showed the degeneration of not only dopaminergic neurons but also serotoninergic neurons [19,21]. PET studies using markers of dopamine storage capacity and serotonin transporter in patients with fatigue have shown serotonergic denervation in the basal ganglia and the limbic circuits including the cingulate gyrus, amygdala, and insular cortex as compared with non-fatigued patients [33]. At the same time, serotonin 5-HT receptors are highly expressed in the visual brain areas [12,24], and serotonin 5-HT1A and 2A receptor binding is increased in the orbitofrontal and temporal cortex [9]. Serotonin 5-HT2A receptors have been implicated in the pathogenesis of visual hallucinations in PD [3,23]. Atypical antipsychotic agents such as quetiapine, which are serotonin 5-HT2A and 2C antagonists [1], have been an effective treatment for hallucinations in PD. A PET study using a marker for serotonin 5-HT2A receptor availability demonstrated increased serotonin 5-HT2A receptor binding in the ventral visual pathway including the bilateral inferior occipital gyrus, inferotemporal cortex, right fusiform gyrus, and insula [3]. Pathologically, 5-HT2A receptor expression was increased in the inferior temporal cortex, and the temporal lobe is likely to be involved in visual processing [23]. These studies showed some near and commonly associated brain areas in patients with fatigue as well as those with hallucinations, particularly in the temporal lobe. Serotonin neurons in the dorsal raphe nuclei project mainly to the basal ganglia, particularly the striatum, but also to the limbic system [35]. Serotonergic alternation contributes to both fatigue and the onset of hallucinations. Thus, fatigue was identified as a risk factor for first-onset hallucinations in the present study.

The subscore for mood or relations with other people on the BFI was significantly decreased in patients with first-onset hallucinations. In contrast, the subscore for walking ability or normal work on the BFI, which is related to physical fatigue, did not significantly differ between patients with and those without hallucinations. In PD, mental fatigue is reported when patients lack motivation and may result from depression

Table 2
Logistic regression analysis for the first-onset hallucinations in patients with Parkinson's disease.

Variables	Crude odds ratio (95% CI)	P	Adjusted odds ratio (95% CI)[a]	P
Age	1.042 (0.973 to 1.116)	0.237		
Male	0.812 (0.297 to 2.218)	0.685		
Log-transformed disease duration	1.532 (0.87 to 2.699)	0.14		
Log-transformed total levodopa equivalent dose	1.327 (0.981 to 1.795)	0.066		
Hoehn–Yahr stage	2.349 (0.967 to 5.705)	0.059		
Total UPDRS score	1.036 (1.001 to 1.073)	0.043*	1.032 (0.995 to 1.071)	0.087
UPDRS part III score	1.04 (0.988 to 1.095)	0.131		
Motor complications	1.385 (0.512 to 3.743)	0.521		
MMSE < 26,	1.038 (0.269 to 4.012)	0.956		
SDS ≧ 50	4.593 (0.483 to 43.627)	0.184		
Zung Self-rating anxiety score ≧ 50	1.432 (0.293 to 6.995)	0.657		
Brief Fatigue Inventory	1.029 (1.004 to 1.055)	0.023*	1.027 (1.001 to 1.053)	0.045*
Log-transformed total PDSS score	1.514 (0.729 to 3.143)	0.266		
Sleep quality on PDSS	1 (0.546 to 1.831)	1		
log-transformed nocturnal motor symptoms on PDSS	1.274 (0.882 to 1.84)	0.197		
Daytime somnolence on PDSS	1 (0.546 to 1.831)	1		
Nightmare	1.21 (0.424 to 3.454)	0.722		
Dream enacting behavior	2.042 (0.532 to 7.829)	0.298		

UPDRS: new revised Unified Parkinson's Disease Rating Scale, PDSS: Parkinson's Disease Sleep Scale, MMSE: Mini-Mental Status Examination, SDS: Zung Self-Rating Depression Scale, a: adjusted for total UPDRS score, and Brief Fatigue Inventory.
* P < 0.05.

[29]. Such mental fatigue might be more closely associated with hallucinations than physical fatigue.

The prevalence of hallucinations in the present longitudinal study was high, with a rate of 49%. Community-based samples have shown a prevalence rate of 16% to 23% in patients with PD, and in prospective cross-sectional studies the rate increased to 22% to 38% [11]. The prevalence rate of hallucinations also increases over time, and longitudinal studies reported that the rate reached 54% after 20 years of follow-up [11].

Sleep disorders are an important risk factor for hallucinations, but we found no association of scores on the PDSS, nightmares, or dream-enacting behavior with first-onset hallucinations. These factors were evaluated at study entry (3 years ago), and if evaluations were performed within a short period from the onset of hallucinations, these factors might have been shown to be related to hallucinations. Concurrent vivid dreams/nightmares accompanied by concurrent acting out of dreams were shown to be strongly associated with the presence of hallucinations, but these factors have no predictive value for the future development of hallucinations [17]. Hallucinations and sleep disorders are distinct behavioral abnormalities with different patterns of progression [17]. Our observations also showed that nightmare or dream-enacting behavior was more often evident in patients with first-onset hallucinations, whereas these factors were not predictors of hallucinations.

We used the BFI to validate fatigue, and the odds ratio was low. The reason for this outcome was that we did not use a specific Parkinson's fatigue scale derived from questionnaires designed for patients with PD [7]. The Parkinson's fatigue scale includes the presence of not only PD-specific physical but also mental fatigue. Depression can trigger or aggravate hallucinations [15] and is closely linked to physical and mental fatigue [18]. The present study evaluated depression by means of the SDS. The Quick Inventory of Depressive Symptomatology (QIDS-J) includes 16 items and is in accordance with the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [28]. The Hamilton depression score has been frequently used as a tool for evaluating depression [20]. These questionnaires can play an important role in better investigating the association of depression with hallucinations. Other limitations in the present study were the small number of hallucinators and the long interval of the face-to-face interviews. If we had used a written dairy for the presence of hallucinations, the number of hallucinations might have increased.

In conclusion, the present study is the first to demonstrate an association of fatigue with the onset of hallucinations. Fatigue, especially mental fatigue, can be a risk factor for future hallucinations.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ensci.2016.04.001.

Funding statement

There was no funding related to our paper.

Competing interest

The authors report no competing interest related to our paper.

References

[1] G.K. Aghajanian, G.J. Marek, Serotonin and hallucinogens, Neuropsychopharmacology 21 (1999) 16S–23S.
[2] G. Alves, T. Wentzel-Larsen, J.P. Larsen, Is fatigue an independent and persistent symptom in patients with Parkinson disease, Neurology 63 (2004) 1908–1911.
[3] B. Ballanger, A.P. Strafella, T. van Eimeren, et al., Serotonin 2A receptors and visual hallucinations in Parkinson disease, Arch Neurol 67 (2010) 416–421.
[4] J. Barnes, A.S. David, Visual hallucinations in Parkinson's disease: a review and phenomenological survey, J Neurol Neurosurg Psychiatry 70 (2001) 727–733.
[5] A.G. Beiske, J.H. Loge, M.J. Hjermstad, et al., Fatigue in Parkinson's disease: frequency and associated factors, Mov Disord 25 (2010) 2456–2460.
[6] A.G. Beiske, E. Svensson, Fatigue in Parkinson's disease: a short update, Acta Neurol Scand Suppl (2010) 190.78–190.81.
[7] R.G. Brown, A. Dittner, L. Findley, et al., The Parkinson fatigue scale, Parkinsonism Relat Disord 11 (2005) 49–55.
[8] K.R. Chaudhuri, S. Pal, A. DiMarco, et al., The Parkinson's disease sleep scale: a new instrument for assessing sleep and nocturnal disability in Parkinson's disease, J Neurol Neurosurg Psychiatry 73 (2002) 629–635.
[9] C.P. Chen, J.T. Alder, L. Bray, et al., Post-synaptic 5-HT1A and 5-HT2A receptors are increased in Parkinson's disease neocortex, Ann N Y Acad Sci 861 (1998) 288–289.
[10] A.J. Cleare, C. Messa, E.A. Rabiner, et al., Brain 5-HT1A receptor binding in chronic fatigue syndrome measured using positron emission tomography and [11C]WAY-100635, Biol Psychiatry 57 (2005) 239–246.
[11] N.J. Diederich, G. Fénelon, G. Stebbins, et al., Hallucinations in Parkinson disease, Nat Rev Neurol 5 (2009) 331–342.
[12] R.H. Dyck, M.S. Cynader, Autoradiographic localization of serotonin receptor subtypes in cat visual cortex: transient regional, laminar, and columnar distributions during postnatal development, J Neurosci 13 (1993) 4316–4338.
[13] S. Fahn, R. Elton, Members of UPDRS Development Committee, in: S. Fahn, C.D. Marsden, D.B. Caine, M. Goldstein (Eds.), Unified Parkinson's Disease Rating Scale, Recent Development in Parkinson's Disease, vol. 2, Macmillan Health Care Information, Florham Park, NJ 1987, pp. 153–163 (293–304).
[14] G. Fénelon, F. Mahieux, R. Huon, et al., Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors, Brain 123 (2000) 733–745.
[15] G. Fénelon, S. Marie, J.P. Ferroir, et al., Musical hallucinations: 7 cases, Rev Neurol (Paris) 149 (1993) 462–467.
[16] Y.Q. Gao, B.C. Pan, W. Sun, et al., Anxiety symptoms among Chinese nurses and the associated factors: a cross sectional study, BMC Psychiatry 12 (2012) 141.
[17] C.G. Goetz, B. Ouyang, A. Negron, et al., Hallucinations and sleep disorders in PD: ten-year prospective longitudinal study, Neurology 75 (2010) 1773–1779.
[18] P. Hagell, L. Brundin, Towards an understanding of fatigue in Parkinson disease, J Neurol Neurosurg Psychiatry 80 (2009) 489–492.
[19] G.M. Halliday, P.C. Blumbergs, R.G. Cotton, et al., Loss of brainstem serotonin- and substance P-containing neurons in Parkinson's disease, Brain Res 510 (1990) 104–107.
[20] J.L. Hedlund, B.W. Viewig, The Hamilton rating scale for depression: a comprehensive review, J Oper Psychiatry 10 (1979) 149–165.
[21] N.A. Hillarp, K. Fuxe, A. Dahlstrom, Demonstration and mapping of central neurons containing dopamine, noradrenaline, and 5-hydroxytryptamine and their reactions to psychopharmaca, Pharmacol Rev 18 (1966) 727–741.
[22] A.J. Hughes, S.E. Daniel, L. Kilford, et al., Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases, J Neurol Neurosurg Psychiatry 55 (1992) 181–184.
[23] P. Huot, T.H. Johnston, T. Darr, et al., Increased 5-HT2A receptors in the temporal cortex of parkinsonian patients with visual hallucinations, Mov Disord 25 (2010) 1399–1408.
[24] R.L. Jakab, P.S. Goldman-Rakic, 5-Hydroxytryptamine2A serotonin receptors in the primate cerebral cortex: possible site of action of hallucinogenic and antipsychotic drugs in pyramidal cell apical dendrites, Proc Natl Acad Sci U S A 95 (1998) 735–740.
[25] F. Kanda, K. Oishi, K. Sekiguchi, et al., Characteristics of depression in Parkinson's disease: evaluating with Zung's self-rating depression scale, Parkinsonism Relat Disord 14 (2008) 19–23.
[26] H. Kataoka, S. Ueno, Low FAB score as a predictor of future falling in patients with Parkinson's disease: a 2.5-year prospective study, J Neurol 262 (2015) 2049–2055.
[27] H. Kataoka, S. Ueno, Predictable risk factors for the feeling of presence in patients with Parkinson's disease, Mov Disord Clin Pract 2 (2015) 407–412.
[28] R.C. Kessler, P. Berglund, O. Demler, et al., The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R), JAMA 289 (2003) 3095–3105.
[29] J.S. Lou, G. Kearns, B. Oken, et al., Exacerbated physical fatigue and mental fatigue in Parkinson's disease, Mov Disord 16 (2001) 190–196.
[30] T.R. Mendoza, X.S. Wang, C.S. Cleeland, et al., The rapid assessment of fatigue severity in cancer patients: use of the Brief Fatigue Inventory, Cancer 85 (1999) 1186–1196.
[31] A. Minguez-Castellanos, F. Escamilla-Sevilla, M.J. Katati, et al., Different patterns of medication change after subthalamic or pallidal stimulation for Parkinson's disease: target related effect or selection bias? J Neurol Neurosurg Psychiatry 76 (2005) 34–39.
[32] A.B. Neikrug, J.A. Avanzino, L. Liu, et al., Parkinson's disease and REM sleep behavior disorder result in increased non-motor symptoms, Sleep Med 15 (2014) 959–966.
[33] N. Pavese, V. Metta, S.K. Bose, et al., Fatigue in Parkinson's disease is linked to striatal and limbic serotonergic dysfunction, Brain 133 (2010) 3434–3443.
[34] S. Perez-Lloret, M. Rossi, M.I. Nouzeilles, et al., Parkinson's disease sleep scale, sleep logs, and actigraphy in the evaluation of sleep in parkinsonian patients, J Neurol 256 (2009) 1480–1484.
[35] M. Politis, C. Loane, Serotonergic dysfunction in Parkinson's disease and its relevance to disability, Sci World J 1 (2011) 1726–1734.
[36] J. Schindehütte, C. Trenkwalder, "Atypical anti-psychotics" are substances of choice in treating drug-induced psychosis (DP) in Parkinson's disease (PD), Clin Neurol Neurosurg 109 (2007) 188–191.
[37] P. Solla, A. Cannas, C.S. Mulas, et al., Association between fatigue and other motor and non-motor symptoms in Parkinson's disease patients, J Neurol 261 (2014) 382–391.
[38] K. Tanaka, K. Wada-Isoe, M. Yamamoto, et al., Clinical evaluation of fatigue in Japanese patients with Parkinson's disease, Brain Behav 4 (2014) 643–649.
[39] W. Tse, Y. Liu, G.M. Barthlen, et al., Clinical usefulness of the Parkinson's disease sleep scale, Parkinsonism Relat Disord 11 (2005) 317–321.
[40] P.O. Valko, D. Waldvogel, M. Weller, et al., Fatigue and excessive daytime sleepiness in idiopathic Parkinson's disease differently correlate with motor symptoms, depression, and dopaminergic treatment, Eur J Neurol 17 (2010) 1428–1436.
[41] S. Yamamoto, Y. Ouchi, H. Onoe, et al., Reduction of serotonin transporters of patients with chronic fatigue syndrome, Neuroreport 15 (2004) 2571–2574.
[42] K. Zhu, J.J. van Hilten, H. Putter, et al., Risk factors for hallucinations in Parkinson's disease: results from a large prospective cohort study, Mov Disord 28 (2013) 755–762.
[43] W.W.K. Zung, A self-rating depression scale, Arch Gen Psychiatry 12 (1965) 63–70.