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Testing an aetiological model of visual hallucinations in Parkinson's disease

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The exact pathogenesis of visual hallucinations in Parkinson's disease is not known but an integrated model has been proposed that includes impaired visual input and central visual processing, impaired brainstem regulation of sleep–wake cycle with fluctuating vigilance, intrusion of rapid eye movement dream imagery into wakefulness and emergence of internally generated imagery, cognitive dysfunction and influence of dopaminergic drugs. In a clinical study, we assessed motor and non-motor function, including sleep, mood, autonomic and global, frontal and visuoperceptive cognitive function in patients with and without visual hallucinations. A subgroup of patients underwent detailed ophthalmological assessment. In a separate pathological study, histological specimens were obtained from cases of pathologically proven Parkinson's disease and a retrospective case notes review was made for reporting of persistent formed visual hallucinations. An assessment of Lewy body and Lewy neurite pathology was carried out in five cortical regions as recommended by diagnostic criteria for dementia with Lewy Bodies and in brainstem nuclei. Ninety-four patients (mean age 67.5 ± 9.5 years) participated in the clinical study of whom 32% experienced visual hallucinations. When corrected for multiple comparisons, patients with visual hallucinations had significantly greater disease duration, treatment duration, motor severity and complications, sleep disturbances, in particular excessive daytime somnolence and rapid eye movement sleep behavioural disorder, disorders of mood, autonomic dysfunction and global, frontal and visuoperceptive cognitive dysfunction. Of the 94 patients, 50 (53%) underwent ophthalmological assessment. There were no differences in ocular pathology between the visual hallucination and non-visual hallucination groups. In a logistic regression model the four independent determinants of visual hallucinations were rapid eye movement sleep behavioural disorder ($P = 0.026$), autonomic function ($P = 0.004$), frontal cognitive function ($P = 0.020$) and a test of visuoperceptive function (object decision; $P = 0.031$). In a separate study, post-mortem analysis was performed in 91 subjects (mean age at death 75.5 ± 8.0 years) and persistent visual hallucinations were documented in 63%. Patients in the visual hallucinations group had similar disease duration but had significantly higher Lewy body densities in the middle frontal ($P = 0.002$) and middle temporal gyri ($P = 0.033$) and transentorhinal ($P = 0.005$) and anterior cingulate ($P = 0.020$) cortices but not parietal cortex ($P = 0.22$). Using a comprehensive assessment of the clinical, demographic and ophthalmological correlates of visual hallucinations in Parkinson's disease, the combined data support the hypothesized model of impaired visual processing, sleep–wake

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dysregulation and brainstem dysfunction, and cognitive, particularly frontal, impairment all independently contributing to the pathogenesis of visual hallucinations in Parkinson's disease. These clinical data are supported by the pathological study, in which higher overall cortical Lewy body counts, and in particular areas implicated in visuoperception and executive function, were associated with visual hallucinations.

Keywords: Parkinson's disease; pathology; cognitive deficits; visual hallucinations; sleep disorders; autonomic dysfunction; ophthalmology

Abbreviations: RBD = rapid eye movement sleep behavioural disorder; REM = rapid eye movement; SCOPA = Scales for Outcome in Parkinson Disease; UPDRS = Unified Parkinson's Disease Rating Scale

Introduction

Epidemiology of visual hallucinations in Parkinson's disease

Visual hallucinations are common in Parkinson's disease with estimates ranging from 16% to 75% (Goetz *et al.*, 2009). The occurrence of visual hallucinations may predict progression to more severe forms of psychosis, increased risk of nursing home placement and development of dementia (Fenelon and Alves, 2010). Previously reported risk factors include older age (Fenelon and Alves, 2010), longer disease duration, greater disease severity (Papapetropoulos *et al.*, 2005; Fenelon and Alves, 2010), cognitive impairment (Merims *et al.*, 2004; Papapetropoulos *et al.*, 2005), particularly frontal lobe (Grossi *et al.*, 2005; Ozer *et al.*, 2007) and visuoperceptive function (Barnes *et al.*, 2003; Ramirez-Ruiz *et al.*, 2006; Meppelink *et al.*, 2008). The role of dopaminergic medication and other Parkinson's disease treatments in the development of visual hallucinations is unclear (Aarsland *et al.*, 1999; Fenelon *et al.*, 2000; Merims *et al.*, 2004; Fenelon and Alves, 2010). Some studies have shown an association of visual hallucinations with co-existing psychiatric disorders, including depression (Sanchez-Ramos *et al.*, 1996; Holroyd *et al.*, 2001; Marsh *et al.*, 2004) and apathy (Mosimann *et al.* 2006), but when other factors are considered, co-existing psychiatric comorbidity appears less important (Fenelon *et al.*, 2000). Autonomic dysfunction such as fall in systolic blood pressure and cardiac sympathetic denervation has also been associated with the presence of visual hallucinations in Parkinson's disease (Williams and Lees, 2005; Oka *et al.*, 2007; Kitayama *et al.*, 2008). In addition, excessive daytime somnolence, sudden onset rapid eye movement (REM) periods and intrusion of episodes of REM sleep during wakefulness and disrupted sleep-wake cycle have been shown to be associated with visual hallucinations in Parkinson's disease (Nomura *et al.*, 2003; Diederich *et al.*, 2005; Whitehead *et al.*, 2008; Goetz *et al.*, 2009).

Pathogenesis of visual hallucinations in Parkinson's disease

Lewy bodies in Parkinson's disease are found in the substantia nigra in association with nigral cell loss but are also found in widespread extra-nigral cortical locations (Braak *et al.*, 2003). A higher Lewy body burden in the temporal lobe and amygdala (Harding *et al.*, 2002*a*, *b*; Papapetropoulos *et al.*, 2006*b*; Kalaitzakis *et al.*, 2009), and in the frontal and parietal cortices (Papapetropoulos *et al.*, 2006*b*) has been associated with visual hallucinations in Parkinson's disease in pathological studies. In addition, several milestones of advanced disease, including dementia and the development of visual hallucinations, have been associated with higher cortical Lewy body scores (Kempster *et al.*, 2010). Functional imaging studies also suggest involvement of these regions in patients with Parkinson's disease with visual hallucinations (Nagano-Saito *et al*, 2004; Oishi *et al.*, 2005; Boecker *et al.*, 2007; Ramirez-Ruiz *et al.*, 2007; Meppelink *et al.*, 2009). These areas are also thought to play an important role in visuoperception. The dual stream hypothesis of visual processing proposes a dorsal stream from the occipital to the parietal lobe specialized for spatial location and a ventral stream involving the temporal lobes and limbic structures for object recognition (Mishkin and Ungerleider, 1982), with white matter tracts projecting to the medial and lateral temporal cortices including the amygdala and parahippocampal gyrus (Catani *et al.*, 2003). As a mechanism for the pathophysiology of visual hallucinations in Parkinson's disease, it has been suggested that impaired object identification through pathology in temporal lobe and limbic structures can lead to disinhibition of internally generated imagery (Diederich *et al.*, 2005; Goetz *et al.*, 2009). Thus, there is evidence to suggest that hallucinations in other conditions as well as in Parkinson's disease are associated with impaired discrimination of external perceptions from internally generated information, referred to as 'reality monitoring', and the medial temporal and frontal lobes have been implicated in this process (Henkel *et al.*, 1998; Barnes *et al.*, 2003).

Integrated hypothesis for visual hallucinations in Parkinson's disease

Taking together the results from clinical, neuropsychological, imaging and pathological studies, a model of imbalance of external and internal inputs and impaired reality monitoring (Diederich *et al.*, 2005, 2009; Goetz *et al.*, 2009) leading to the development of visual hallucinations has therefore been suggested, including: (i) impaired visual input and central visual processing; (ii) impaired brainstem regulation of the sleep–wake cycle with fluctuating vigilance, intrusion of REM dream imagery into wakefulness and emergence of internally generated imagery; (iii) cognitive

dysfunction including areas implicated in discriminating internal and external generated information (reality monitoring); and (iv) influence of dopaminergic drugs on mesolimbic and visual processing pathways (Goetz *et al*., 2009).

We undertook studies to examine the *in vivo* and pathological validity of this proposed hypothesis, taking into account all clinical and pathological features that have been proposed to contribute to visual hallucinations in Parkinson's disease. We therefore aimed to: (i) determine the demographic and clinical variables associated with visual hallucinations in Parkinson's disease including age, disease duration, dopaminergic medication, sleep disorders [daytime somnolence, nocturnal insomnia and rapid eye movement sleep behavioural disorder (RBD)], current psychopathology (depression, anxiety and apathy), and presence of executive and global cognitive dysfunction; (ii) determine the relative importance of cortical visual processing and presence of ophthalmic pathology in the aetiology of visual hallucinations in Parkinson's disease; (iii) to validate an integrated model of visual hallucinations in Parkinson's disease including abnormal visual processing, RBD and brainstem dysfunction, dysexecutive cognitive impairment and dopaminergic medication; and (iv) determine the distribution of Lewy body and Lewy neurite load as a marker of disease involvement at different cortical regions involved in visual processing (temporal lobes and limbic structures including the amygdalae) and regions implicated in reality discrimination (medial temporal and frontal lobes).

Subject and methods

Clinical study participants

Consecutive patients who fulfilled UK Brain Bank criteria for Parkinson's disease (Gibb and Lees, 1989) were recruited from Parkinson's disease outpatient clinics. Subjects underwent a face-to-face interview, comprising clinical examination and physician-administered questionnaires in clinic, and were given further questionnaires to complete at home. A subgroup of patients, who consented to an additional appointment, also had a full ophthalmological assessment. Visual hallucinations were defined as persistent formed visual hallucinations and illusions. Patients with brief episodes of hallucinations related to sepsis or alteration of medication were excluded.

Measures

The following measures were used: (i) Unified Parkinson's Disease Rating Scale (UPDRS; Fahn *et al.*, 1987); (ii) non-motor scales and assessments including Scales for Outcome in Parkinson Disease (SCOPA) Sleep scale (Marinus *et al.*, 2003*a*), International Classification of Sleep Disorders, Revised diagnostic criteria for RBD (American Academy of Sleep Medicine, 2001), Lille Apathy Rating Scale (Sockeel *et al.*, 2006), Hamilton Depression rating scale (Schwab *et al.*, 1967), Frontal Assessment Battery (Dubois *et al.*, 2000), SCOPA cognitive scale (Marinus *et al.*, 2003*b*), SCOPA autonomic scale (Visser *et al*., 2004), University of Miami Parkinson's disease hallucinations questionnaire (Papapetropoulos 2008); (iii) (in a subgroup) ophthalmological measures including logarithm of minimal angle of visuospatial resolution (logMAR) visual acuity testing (Sprague *et al.*, 1989) (logMAR of zero is equivalent to normal visual acuity [6/6] on Snellen chart, with negative scores representing better than normal acuity and positive scores poorer acuity), Goldmann kinetic perimetry (Niederhauser and Mojon, 2002), mean peripheral field diameter expressed as mean radial degrees, retinal photography, descriptive assessment of cataract presence, location (nuclear, cortical, subcapsular) and degree of opacity; (iv) (in a subgroup) tests for visual agnosia, the Birmingham Object Recognition Battery (Riddoch and Humphreys, 1993) including low level aspects of visual perception (same-different matching of elemental features such as orientation, length and object size), higher visual perception (identification of overlapping images, matching objects from usual and unusual viewpoints and identification of objects from minimal features) and stored perceptual knowledge (object decision tasks; discrimination between pictures of real objects and non-objects made by combining parts of different real objects; Humphreys *et al.*, 1997) and semantic knowledge testing [associative matching; deciding which of two reference pictures (e.g. a screw and a nail) is most associated with a target picture (a screwdriver), Humphreys *et al*., 1997].

Ethical approval for the clinical studies was obtained from the local research ethics committees.

Pathological study

In a separate study, histological specimens were obtained from cases of pathologically proven Parkinson's disease archived at the Queen Square Brain Bank for Neurological Diseases. The London Multi-Centre Research Ethics Committee has approved procedures for the donation of brains to the Queen Square Brain Bank as well as retention of and access to clinical records. A retrospective case notes review was made for reporting of persistent formed visual hallucinations. Demographic and disease characteristics including age, sex, disease duration, dopaminergic medication and documented presence of cognitive impairment were recorded. An approximation of the cumulative life-time L-DOPA amount was made based on the information available in the patient records.

Neuropathological assessment

After fixation in 10% buffered formalin, the brains were examined by a neuropathologist and sampled in accordance with the standardized protocols of the Queen Square Brain Bank. In compliance with established criteria for the neuropathological diagnosis of Parkinson's disease (Ince *et al.*, 2008), brain samples from selected regions were embedded in paraffin. Eight μm-thick tissue sections were cut, deparaffinized and rehydrated, followed by pre-treatment with formic acid and pressure-cooking in citrate buffer at pH 6.0. Following epitope unmasking, monoclonal antibody to α-synuclein (clone KM51, dilution 1:1000; Novocastra) was applied and incubated overnight at 4°C. For detection, Histostain SP kit (Zymed) was used with Romulin AEC chromogen (Biocare Medical). Semi-quantitative assessment of α-synuclein immunoreactive Lewy body-type pathology was carried out in

five cortical regions, frontal [middle frontal gyrus, Brodmann's area (BA) 8/9], temporal (middle temporal gyrus, BA 21), parietal (inferior parietal lobule BA 40), entorhinal (parahippocampal gyrus, BA 28) and cingulate (anterior cingulate, BA 24) cortices as recommended by the consensus diagnostic criteria for dementia with Lewy bodies (McKeith *et al.*, 2005) and rated as follows: 1 = mild (sparse Lewy bodies at × 100 magnification); 2 = moderate (1 to 3 Lewy bodies at ×100 magnification); 3 = severe (⩾4 Lewy bodies at ×200 magnification); 4 = very severe (numerous Lewy bodies and Lewy neurites at ×200 magnification). In addition, all Lewy bodies were systematically counted within the same five cortical areas of interest and these counts were adjusted to the surface area (Lewy bodies/mm^2) using Image-Pro Plus software package (MediaCybernetics). The total cortical Lewy body density was determined as the sum of counts in the five cortical areas divided by a sum of respective surface areas. In addition, in the amygdala, the number of α-synuclein immunoreactive Lewy bodies per ×200 microscopic field (field diameter 1 mm) was determined in the region with the greatest Lewy body density. In the brainstem, α-synuclein immunopositive Lewy bodies were counted unilaterally within entire nuclei and assessed following an arbitrary grading system: in substantia nigra, + ⩽25 Lewy bodies; + + = 25–50 Lewy bodies; + + + ⩾50 Lewy bodies, in locus coeruleus and dorsal motor nucleus of vagus (dmV), + = 1–9 Lewy bodies; + + = 10–19 Lewy bodies, + + + = >20 Lewy bodies. The α-synuclein immunoreactive Lewy neurites in each region were rated semi-quantitatively as: 0 = absent, 1 = sparse; 2 = moderate; and 3 = frequent. Finally, each case was also classified according to Braak Parkinson's disease stage (ranging from 0 to 6) depending on the topographic distribution of α-synuclein immunoreactive inclusions (Braak *et al.*, 2003). All pathological analyses were done blinded to the clinical data.

Statistical analysis

Data were entered into the statistical programme SPSS version 17.0 (SPSS, Inc.) and inspected for normality of distribution. Results were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. As the data were mostly not normally distributed, we used non-parametric tests for analysis. For comparison of visual hallucinations and non-visual hallucinations groups, data were expressed as median and interquartile range and non-parametric (Mann–Whitney U) analysis was performed. Categorical data were analysed using chi-square or Fisher's exact test. The univariate analysis was used to select variables for inclusion in the multivariate regression analysis. A binary logistic regression analysis was performed to assess the effect of different clinimetric variables (treatment duration, UPDRS part III, UPDRS part IV, RBD, SCOPA-sleep daytime, Hamilton depression rating scale, SCOPA autonomic scale, Frontal Assessment Battery, SCOPA cognitive scale-executive score, Birmingham Object Recognition Battery object decision, minimal feature match, association match and overlapping images) on the main dichotomous outcome measure (presence or absence of visual hallucinations).

Results

Clinical study

Ninety-four patients participated in the study, of whom five (5%) had evidence of global dementia (Mini-Mental State Examination ⩽24). No patient fulfilled clinical criteria for dementia with Lewy bodies (McKeith *et al.*, 2005), with onset of dementia before or within 1 year of onset of parkinsonism. Thirty patients had experienced visual hallucinations and/or illusions (referred to as visual hallucinations henceforth). Three of five patients with dementia had visual hallucinations whereas the remainder with visual hallucinations were non-demented (Mini-Mental State Examination >24). The type of visual experiences reported by patients were: illusions of presence (n = 18), illusions of passage (n = 26), visual illusions (n = 27) and formed visual hallucinations (n = 22). Six patients also reported acoustic, five tactile and three olfactory hallucinations. Of 30 patients, 27 with visual hallucinations completed the University of Miami Parkinson's disease hallucinations questionnaire. Of 27 patients, 14 (52%) had very frequent hallucinations (⩾1 per day). In terms of visual hallucinations content, 19/27 (70%) reported seeing animals, 18/27 (67%) saw people, 15/27 (56%) whole faces, 13/27 (48%) insects or reptiles, 13/27 (48%) objects and 6/27 (22%) fragmented faces. In only one patient visual hallucinations were not formed or difficult to describe. In 23/27 (85%) the visual experience was familiar. Images were solid (rather than transparent) in 24/27 (89%), moving in 15/27 (56%), coloured in 15/27 (56%) and made a sound in 3/27 (11%).

Demographic and clinical correlates of patients with Parkinson's disease with visual hallucinations

After adjustment for multiple comparisons (n = 29 comparisons, Bonferroni correction, significance $P < 0.0017$) disease duration, treatment duration, dopaminergic medication dose (levodopa equivalent units), motor function (UPDRS) and motor complications (UPDRS total part IV and percentage daily OFF time) were significantly associated with visual hallucinations in Parkinson's disease (Table 1). A higher proportion of patients with visual hallucinations were taking levodopa (87 versus 58%, $P < 0.009$) but this was not significant for multiple corrections and there was no association with other medication (ergot or non-ergot dopamine agonists, amantadine, catechol-*O*-methyl transferase inhibitors, monoamine oxidase-B inhibitors, anticholinergics, cholinesterase inhibitors or atypical antipsychotics). Significant associations with non-motor aspects of Parkinson's disease, after correction for multiple comparisons, included excessive daytime somnolence (SCOPA sleep-daytime) and RBD, depression (Hamilton Depression rating scale) and overall autonomic dysfunction (SCOPA autonomic scale) (Table 1) and gastrointestinal, urinary and cardiovascular subscales (all $P \leqslant 0.0001$). In addition, visual hallucinations were associated with global cognitive impairment scores (SCOPA cognitive scale total) but in particular frontal cortical dysfunction (Frontal Assessment Battery total score, and

Table 1 Clinical findings of patients with Parkinson's disease with and without visual hallucinations

	With visual hallucinations ($n = 30$) Median (interquartile range) or n (%)	Without visual hallucinations ($n = 64$) Median (interquartile range) or n (%)	P-value (Mann–Whitney U or χ^2-test)
Demographics			
Age (years)	71.0 (65.5 to 74.3)	66.5 (59.0 to 74.0)	0.018
Sex (male), n (%)	24/30 (80)	41/64 (64)	0.15
Disease duration (years)	11.2 (5.3 to 15.8)	3.4 (1.8 to 7.7)	**0.0001**
Treatment duration (years)	10.5 (4.8 to 15.4)	2.8 (0.2 to 7.0)	**<0.0001**
LEU (mg)	750 (400 to 1026)	300 (100 to 739)	**0.0012**
UPDRS part III	38.0 (28.5 to 48.0)	26.0 (17 to 33.8)	**<0.0001**
UPDRS part IV	6.0 (3.0 to 8.0)	1.0 (0.0 to 4.0)	**<0.0001**
'Off' (% of waking day)	18.0 (6.8 to 31.3)	0.0 (0.0 to 6.8)	**<0.0001**
Dyskinesia (%)	0.0 (0.0 to 31.8)	0.0 (0.0 to 3.0)	0.045
Non-motor scales			
REM sleep disorder, n (%)	16/30 (53)	11/64 (17)	**0.0005**
SCOPA-sleep-night	6.0 (3.0 to 11.0)	3.0 (1.0 to 7.0)	0.012
SCOPA-sleep-day	7.5 (4.0 to 12.3)	3.0 (2.0 to 6.0)	**<0.0001**
LARS-total	−21 (−27 to −16.5)	−26.5 (−31.0 to −22.0)	0.0096
HDRS	5.0 (2.0 to 8.0)	2.0 (0 to 5.0)	**0.0002**
SCOPA-AUT total	21.5 (16.8 to 26.3)	11.0 (8.0 to 17.0)	**<0.0001**
Cognition			
FAB total	14.0 (12.0 to 16.0)	17.0 (15.0 to 17.0)	**<0.0001**
SCOPA-COG total	22.0 (17.8 to 25.5)	26.0 (23.0 to 31.8)	**0.0005**
SCOPA-COG memory	7.5 (5.0 to 9.3)	9.0 (7.0 to 12.8)	0.017
SCOPA-COG attention	4.0 (3.0 to 4.0)	4.0 (4.0 to 4.0)	0.026
SCOPA-COG executive	7.0 (5.5 to 9.0)	9.5 (8.3 to 11.0)	**<0.0001**
SCOPA-COG visuospatial	3.0 (2.0 to 5.0)	4.0 (3.0 to 5.0)	0.13
Visuoperceptive function			
BORB size match	26.0 (23.5 to 27.0)	27.0 (26.0 to 28.0)	0.048
BORB length match	25.0 (23.0 to 27.0)	26.0 (25.0 to 27.0)	0.12
BORB orientation match	25.0 (23.0 to 25.5)	26.0 (25.0 to 27.0)	0.0064
BORB foreshortened	24.0 (22.0 to 25.0)	24.0 (24.0 to 25.0)	0.045
BORB minimal feature	24.0 (23.0 to 25.0)	25.0 (25.0 to 25.0)	**0.0006**
BORB overlapping	36.0 (32.0 to 39.0)	40.0 (38.3 to 40.0)	**<0.0001**
BORB association match	28.0 (26.0 to 30.0)	30.0 (29.0 to 30.0)	**0.0002**
BORB object decision	23.0 (21.5 to 24.5)	26.0 (25.0 to 28.0)	**<0.0001**

Variables that reach statistical significance when corrected for multiple comparisons (Bonferroni correction; $n = 29$; $P < 0.0017$) are given in bold. BORB scores based on subgroup, 81 of 94 (86%) patients.
BORB = Birmingham Object Recognition Battery; FAB = Frontal Assessment Battery; HDRS = Hamilton Depression Rating Scale; LARS = Lille Apathy Rating Scale; LEU = levodopa equivalent units; SCOPA-AUT = SCOPA autonomic scale; SCOPA-COG = SCOPA cognitive scale.

SCOPA cognitive scale executive subscore, Table 1). Of 94 patients, 81 (86%) were assessed using the Birmingham Object Recognition Battery. Several tests of visuoperceptive cortical function including Birmingham Object Recognition Battery object decision, overlapping images, minimal feature match and association match were associated with visual hallucinations. In contrast, there was no clear association of visual hallucinations with lower-level visuoperceptual tasks on the Birmingham Object Recognition Battery and visuospatial tasks on the SCOPA cognitive scale.

Ophthalmological assessments

Of 94 participants, 50 (53%) underwent full ophthalmological assessment including 23/30 (77%) participants with visual hallucinations. There were no differences in disease duration, levodopa equivalent units, Mini-Mental State Examination and UPDRS between participants and non-participants in ophthalmological substudy; however patients undergoing ophthalmological assessments were older ($P = 0.01$). The ophthalmological and visuoperceptive variables were compared between patients with visual hallucinations and those without. There were no differences in the ophthalmological parameters tested between the visual hallucinations and non-visual hallucinations group (Table 2). However, in this smaller subgroup several of the visuoperceptive variables (minimal feature match, overlapping images, object decision, association match, size match and orientation match) were still more impaired ($P < 0.05$) in the group of patients with hallucinations, with minimal feature match and

Table 2 Ophthalmological findings and visuoperceptive measures in Parkinson's disease patients with or without visual hallucinations

	With visual hallucinations ($n = 23$) Median (interquartile range) or n (%)	Without visual hallucinations ($n = 27$) Median (interquartile range) or n (%)	P-value (Mann–Whitney U or χ^2-test)
Ophthalmology findings			
VA right uncorrected	0.27 (0.14–0.55)	0.28 (0.10–0.46)	0.69
VA left uncorrected	0.25 (0.12–0.48)	0.20 (0.10–0.40)	0.61
VA right corrected	0.16 (0.04–0.30)	0.14 (0.02–0.22)	0.46
VA left corrected	0.20 (0.06–0.30)	0.08 (0.0–0.20)	0.076
Fields right (MRD)	46.8 (41.7–48.9)	46.3 (37.9–49.7)	0.80
Fields left (MRD)	45.5 (39.5–49.3)	46.9 (40.5–50.5)	0.44
Cataract right, n (%)	14/23 (61)	14/27 (52)	0.58
Cataract left, n (%)	14/23 (61)	14/27 (52)	0.58
Macular degeneration R, n (%)	1/22 (5)	5/27 (19)	0.20
Macular degeneration L, n (%)	1/22 (5)	5/27 (19)	0.20
Corneal pathology R, n (%)	1/23 (4)	1/27 (4)	1.00
Corneal pathology L, n (%)	1/23 (4)	0/27 (0)	0.46
Optic pathology (any), n (%)	17/23 (74)	17/27 (63)	0.55
Visuoperceptual function[a]			
BORB object decision	23.0 (21.0–25.0)	26.0 (23.0–27.0)	0.0026
BORB length match	25.0 (23.0–27.0)	26.0 (25.0–27.0)	0.072
BORB foreshortened	24.0 (22.0–25.0)	24.0 (24.0–25.0)	0.23
BORB minimal feature	24.0 (23.0–25.0)	25.0 (25.0–25.0)	**0.0011**
BORB association	28.0 (26.0–30.0)	30.0 (28.0–30.0)	0.008
BORB size match	26.0 (23.0–27.0)	27.0 (26.0–28.0)	0.036
BORB orientation	25.0 (23.0–25.0)	26.0 (25.0–27.0)	0.022
BORB overlapping	36.0 (33.0–39.0)	40.0 (38.0–40.0)	**0.0014**

a Only includes those patients who had ophthalmological assessments.
Variables that reach statistical significance when corrected for multiple comparisons (Bonferroni correction; n = 21; $P < 0.0024$) are given in bold.
BORB = Birmingham Object Recognition Battery; L = left; MRD = mean radial degrees; R = right; VA = visual acuity (Logarithm of Minimal Angle of Resolution [logMAR]).

overlapping images scales meeting significance for multiple comparisons (Bonferroni correction, 21 comparisons, $P < 0.0024$, Table 2).

Multivariate analysis of clinical, cognitive and ophthalmological variables and visual hallucinations

All variables that were associated with visual hallucinations in the univariate analyses (excluding collinear variables where scale with the strongest association was chosen) were added to the regression analysis (treatment duration, UPDRS part III, UPDRS part IV, RBD, SCOPA sleep daytime, Hamilton depression rating scale, SCOPA autonomic scale, Frontal Assessment Battery, SCOPA cognitive scale-executive score, Birmingham Object Recognition Battery object decision, minimal feature match, association match and overlapping images). The four independent determinants of visual hallucinations in Parkinson's disease were RBD ($P = 0.026$), SCOPA autonomic scale ($P = 0.004$), SCOPA cognitive scale executive ($P = 0.020$) and Birmingham Object Recognition Battery object decision ($P = 0.031$) (Table 3), and overall predicted 67% of the variability in the regression model.

Table 3 Factors associated with visual hallucinations in binary logistic regression analysis

Predictive factor	Odds ratio (95% CI)	P-value
RBD	6.18 (1.24–30.78)	0.026
SCOPA-AUT	1.16 (1.05–1.28)	0.004
SCOPA-COG-executive	0.63 (0.43–0.93)	0.020
BORB-object decision	0.66 (0.46–0.96)	0.031

BORB = Birmingham Object Recognition Battery; CI = confidence interval; SCOPA-AUT = SCOPA autonomic scale; SCOPA-COG = SCOPA cognitive scale. RBD = REM sleep behavioural disorder.

Clinicopathological analysis of visual hallucinations

Post-mortem analysis was performed in 91 subjects. Amygdala analysis was performed in a subset of 68 patients (43 with and 25 without hallucinations) where pathological samples were adequate. On retrospective case notes examination, persistent formed visual hallucinations were found in 57/91 (63%). The visual hallucinations and non-visual hallucinations did not differ in terms of demographic characteristics, including age

and disease duration (Table 4), however, patients with visual hallucinations were significantly more likely to be cognitively impaired ($P = 0.004$). Patients with visual hallucinations had significantly higher Lewy body densities, particularly in the middle frontal gyrus and transentorhinal cortices with higher counts also in the total, middle temporal gyrus and anterior cingulate cortices but not inferior parietal cortex (Table 4). Semi-quantitative Lewy neurite density scores did not differ in any of the cortical locations sampled, although there was a trend for higher Lewy neurite density in the temporal cortex ($P = 0.056$). There was no significant difference in semi-quantitative Lewy neurite or Lewy body scores in the brainstem nuclei assessed (substantia nigra, locus coeruleus and dorsal motor nucleus of vagus). In the visual hallucinations group, the majority were Braak stage 6 (72%) whereas in the non-visual hallucinations group the majority were Braak stage $\leqslant 5$ (65%), $P = 0.002$. In the subgroup with amygdala analysis, there was no difference in amygdala Lewy body density between the visual hallucinations ($n = 43$) and non-visual hallucinations ($n = 25$) groups ($P = 0.69$); however, there was significantly higher total cortical ($P = 0.027$) and particularly middle frontal gyrus Lewy body density ($P = 0.006$) in association with visual hallucinations in this subgroup.

Discussion

This study supports an integrative model of pathogenesis of visual hallucinations in Parkinson's disease, examining the diverse abnormalities reported in clinical, neurophysiological and imaging studies of visual hallucinations in Parkinson's disease. In keeping with previous work, we found that visual hallucinations in our Parkinson's disease population were associated with older age and longer disease duration (Sanchez-Ramos *et al.*, 1996; Papapetropoulos *et al.*, 2005; Fenelon and Alves, 2010) and greater disease severity (Holroyd *et al*., 2001; Papapetropoulos *et al*., 2005). Using a comprehensive assessment of the clinical, demographic, ophthalmological and pathological correlates of visual hallucinations in Parkinson's disease, the combined data support a model of impaired visual processing, sleep–wake dysregulation and brainstem dysfunction and cognitive impairment.

Visual pathways

Examining different aspects of the visual pathways, we did not find evidence to support ophthalmic factors such as impaired visual acuity, reduced visual fields, cataracts, macular degeneration and corneal or other optic pathology contributing to visual

Table 4 Pathological study of Lewy body density, distribution in specimens archived at the Queen Square Brain Bank for Neurological Diseases

	With visual hallucinations ($n = 57$) Median (interquartile range) or *n* (%)	Without visual hallucinations ($n = 34$) Median (interquartile range) or *n* (%)	*P*-value (Mann–Whitney U or χ^2-test)
Demographics			
Age at onset (years)	60.0 (53.6–69.1)	59.4 (53.0–66.2)	0.64
Age at death (years)	76.4 (70.3–81.6)	73.5 (68.5–80.8)	0.27
Disease duration (years)	16.5 (9.0–21.5)	13.4 (9.3–19.7)	0.39
Sex (male), *n* (%)	42/57 (74)	21/34 (62)	0.23
Cumulative levodopa dose ($\times 10^6$ mg)	2.5 (1.1–5.3)	2.5 (0.8–5.3)	0.71
Maximum levodopa dose (mg)	700 (500–1050)	750 (500–1000)	0.95
Ergot agonist use, *n* (%)	18/57 (32)	13/34 (38)	0.52
Non-ergot agonist use, *n* (%)	32/57 (56)	18/34 (53)	0.77
Apomorphine use, *n* (%)	16/57 (28)	6/34 (18)	0.26
COMT inhibitor use, *n* (%)	9/57 (16)	6/34 (18)	0.82
Selegiline use, *n* (%)	31/57 (54)	21/34 (62)	0.49
Amantadine use, *n* (%)	12/57 (21)	7/34 (21)	0.96
Anti-cholinergic use, *n* (%)	29/57 (51)	16/34 (47)	0.73
[a]Cognitive impairment, *n* (%)	45/52 (87)	16/32 (50)	0.0004
Pathological data—Lewy body density			
Parietal cortex (LB/mm^2)	0.00 (0.00–0.06)	0.00 (0.00–0.00)	0.22
Frontal cortex (LB/mm^2)	0.08 (0.00–0.43)	0.00 (0.00–0.07)	0.002
Temporal cortex (LB/mm^2)	0.15 (0.04–0.43)	0.06 (0.00–0.22)	0.033
Cingulate cortex (LB/mm^2)	0.82 (0.23–2.02)	0.38 (0.07–0.98)	0.020
Entorhinal cortex (LB/mm^2)	0.85 (0.28–2.74)	0.27 (0.06–1.00)	0.005
Total cortex (LB/mm^2)	0.40 (0.16–0.86)	0.17 (0.03–0.43)	0.004

Presence of persistent formed visual hallucinations determined from retrospective case notes review.
a Smaller sample ($n = 84$) in whom reliable impression of cognitive status could be made on retrospective case notes review.
COMT = catechol-*O*-methyl transferase; LB = Lewy body.

hallucinations in Parkinson's disease overall. This is in contrast to previous studies of visual hallucinations associated with poor visual acuity (Holroyd *et al*., 2001; Matsui *et al*., 2006) and ocular pathology (Fenelon *et al*., 2000). We did not examine subtle retinal abnormalities using contrast sensitivity or colour discrimination, which has been shown in previous studies to be more prevalent in patients with visual hallucinations than without (Diederich *et al*., 1998), but visual acuity, visual fields and standard optic examinations did not show any differences in this study. Visuospatial tasks that are processed through the parietal lobes (Parks *et al*., 2010) and lower level visuoperceptive tasks related to posterior temporal lobe areas (Bright *et al*., 2005) also did not differ between patients with and without visual hallucinations in Parkinson's disease. However, several higher level visuoperceptive tasks, which implicate the anteromedial temporal cortex, including the entorhinal cortex (Bright *et al*., 2005), were significantly different even when corrected for multiple comparisons. This is consistent with neuropsychological studies demonstrating impaired visuoperceptive function in patients with Parkinson's disease with visual hallucinations (Barnes *et al*., 2003; Ramirez-Ruiz *et al*., 2006; Meppelink *et al*., 2008) and functional imaging studies demonstrating involvement of extrastriate visual processing pathways (Oishi *et al*., 2005; Boecker *et al*., 2007; Ramirez-Ruiz *et al*., 2007; Meppelink *et al*., 2009). These data suggest that impairment of cortical visuoperceptive function is more likely to be involved in the pathogenesis of visual hallucinations in the majority of patients with Parkinson's disease than optic pathology, although this may be relevant in individual patients where this has been reported (Holroyd *et al*., 2001; Fenelon *et al*., 2000; Matsui *et al*., 2006). Our logistic regression results also support the importance of associative visuoperceptive dysfunction, rather than constructional visuospatial dysfunction or lower level apperceptive visual agnosia in the development of visual hallucinations.

Our findings of impairment of higher cortical function in visual pathways in neuropsychological testing were also supported by results of our pathological study. Patients with visual hallucinations demonstrated higher overall cortical Lewy body density with significantly increased Lewy body density in the middle temporal gyrus, anterior cingulate gyrus and particularly the middle frontal gyrus and transentorhinal cortices consistent with previous pathological studies showing higher Lewy body counts in temporal lobe structures in visual hallucinations (Harding *et al*., 2002*a*; Papapetropoulos *et al*., 2006*b*). Additionally there was a trend to higher Lewy neurite density in the temporal cortex. On the other hand, in contrast to previous studies, no increased Lewy body density was found in patients with visual hallucinations in the amygdala (Harding *et al*., 2002*a, b*; Papapetropoulos *et al*., 2006*b*; Kalaitzakis *et al*., 2009) or parietal cortex (Papapetropoulos *et al*., 2006*b*). Kalaitzakis *et al*. (2009) found α-synuclein burden in the amygdala to be strongly related to visual hallucinations but only in those Parkinson's disease cases with concomitant dementia, implicating that α-synuclein pathology in this region is not related to the presence of visual hallucinations *per se* but moreover to dementia.

Sleep–wake regulation and brainstem function

This study also demonstrated significant impairment of the brainstem-regulated sleep–wake cycle with excessive daytime somnolence and increased prevalence of RBD in patients with Parkinson's disease with visual hallucinations. This is consistent with previous studies showing higher prevalence of polysomnographic abnormalities and RBD in visual hallucinations (Comella *et al*., 1993; Manni *et al*., 2002; Nomura *et al*., 2003). Brainstem locations implicated in REM sleep include the dorsolateral tegmental and pedunculopontine nuclei (Kalia, 2006). We have also shown that visual hallucinations are associated with autonomic dysfunction including gastrointestinal, urinary and cardiovascular function. This is consistent with previous studies, where autonomic function has been associated with visual hallucinations (Williams and Lees, 2005; Oka *et al*., 2007; Kitayama *et al*., 2008). Autonomic impairment in Parkinson's disease can be mediated by central brainstem (Lewy body deposition in and degeneration of brainstem nuclei, such as the dorsal vagal nucleus) and peripheral (i.e. cardiac sympathetic denervation) mechanisms. Autonomic dysfunction is associated with RBD, for example abnormal cardiac scintigraphy has been demonstrated in idiopathic RBD (Miyamoto *et al*., 2006). In our clinical study, presence of RBD and autonomic impairment were significant independent predictors in a regression model and this is supportive of greater involvement of brainstem function in patients with Parkinson's disease with visual hallucinations. Furthermore, visual hallucinations in Parkinson's disease resemble the complex peduncular (Lhermitte's) hallucinations (colourful images of people or animals with clear sensorium), which have been described secondary to lesions of the rostral brainstem, the thalamus and striatocapsular regions (Benke, 2006), and are associated with disrupted sleep architecture. Peduncular hallucinations are thought to result from disruption of ascending reticular systems and thalamocortical circuits involved in sleep–wake cycles and alertness (Benke, 2006). In our pathological study higher Lewy body or Lewy neurite densities were not demonstrated in the brainstem nuclei sampled (substantia nigra, locus coeruleus and dorsal nucleus of the vagus). However, other brainstem nuclei that may be relevant to sleep–wake cycle pathology such as lateral tegmental and pedunculopontine tegmental nuclei were not examined in this study and further pathological studies in these areas will be required to clarify to the role of brainstem Lewy body in the pathogenesis of visual hallucinations in Parkinson's disease.

Cognitive impairment

Global cognitive impairment, in the clinical study and retrospective record analysis in the pathological study, was associated with visual hallucinations, consistent with previous literature (Merims *et al*., 2004; Papapetropoulos *et al*., 2005). In addition, frontal lobe function was significantly worse in the group with visual hallucinations, and was an important contributory factor in a regression model to predict presence of visual hallucinations. This is in keeping with previous neuropsychological (Grossi *et al*., 2005; Ozer *et al*., 2007), functional imaging

(Nagano-Saito *et al.*, 2004; Ramirez-Ruiz *et al.*, 2008) and pathological (Papapetropoulos *et al.*, 2006*b*) studies, which showed impairment in frontal lobe function in hallucinating patients compared with those without visual hallucinations. Furthermore, the pathological data in this study confirmed higher Lewy body density in the frontal cortex in patients with visual hallucinations than without, as well as higher total cortical Lewy body density.

Integrated hypothesis

In an integrated analysis of all factors studied in the clinical sample, visual hallucinations in Parkinson's disease were associated with, and independently predicted by, impaired higher visuoperceptive function, particularly implicating the ventral visual pathway, sleep–wake cycle disruption and autonomic dysfunction implicating brainstem dysfunction, and dysexecutive cognitive dysfunction. Similar to previous cross-sectional studies, medication did not contribute further to prediction of occurrence of visual hallucinations (Aarsland *et al.*, 1999; Fenelon *et al.*, 2000; Holroyd *et al.*, 2001; Merins *et al.*, 2004; Fenelon and Alves, 2010), suggesting that other factors modify the impact of dopaminergic medication on visual hallucinations or that this effect is small compared with other factors. The pathological study also supported the important role of frontal and temporal cortical dysfunction, and particularly the involvement of the areas in the ventral visual pathways and areas implicated in reality discrimination.

There are some methodological limitations to this study. The pathological study is limited by the retrospective nature of the clinical data, and a selection bias is expected in a brain-bank post-mortem series. However, cases were chosen based on the availability of adequate clinical data regarding the presence or absence of visual hallucinations. Pathological data were not available for all areas implicated in visual processing, in particular there was no assessment of retinal pathology or regions such as the primary visual cortex. The role of Lewy body deposition in the pathogenesis of Parkinson's disease remains unclear. The proposed sequential staging of topographical involvement of Lewy body pathology in Parkinson's disease (Braak *et al.*, 2003) has not been uniformly confirmed in pathological series and widespread cortical Lewy body pathology has been demonstrated in elderly individuals without neuropsychiatric correlates (Parkkinen *et al.*, 2008; Jellinger, 2009). Attributing non-motor symptoms such as visual hallucinations in Parkinson's disease to regional cortical Lewy body distribution and density, in the absence of clearly demonstrated cell death, should be interpreted cautiously and requires further clarification (Parkkinen *et al.*, 2008; Jellinger, 2009). Visual hallucinations are associated with advanced disease and therefore, in the clinical study, participants could not be matched for disease duration or severity. In order to reduce possibility of alpha errors, strict Bonferroni correction was made in making statistical comparisons. This correction may, however, discount valid weaker associations.

In conclusion, the results support the proposed integrated model of pathogenesis of visual hallucinations through dysregulation in gating and filtering of external perception and internal image production, aberrant activation of associative visual and frontal cortex, lack of suppression or spontaneous emergence of internally generated imagery, intrusion of REM dreaming imagery into wakefulness and dysfunction of the brainstem filtering capacities (Diederich *et al*, 2005; Goetz *et al*., 2009). While ophthalmic abnormalities and medication-related factors may play a role in individual patients, these were not found to make a major contribution to this overall model of visual hallucinations in Parkinson's disease.

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