

Visuoperceptive region atrophy independent of cognitive status in patients with Parkinson's disease with hallucinations

Jennifer G. Goldman,¹ Glenn T. Stebbins,¹ Vy Dinh,² Bryan Bernard,¹ Doug Merkitch,¹ Leyla deToledo-Morrell¹ and Christopher G. Goetz¹

1 Rush University Medical Center, Department of Neurological Sciences, Chicago, IL, USA

2 University of Wisconsin, School of Medicine and Public Health, Madison, WI, USA

Correspondence to: Jennifer G. Goldman, MD, MS,
Rush University Medical Center,
Department of Neurological Sciences,
1725 W. Harrison Street, Suite 755,
Chicago, IL 60612,
USA
E-mail: Jennifer_G_Goldman@rush.edu

Visual hallucinations are frequent, disabling complications of advanced Parkinson's disease, but their neuroanatomical basis is incompletely understood. Previous structural brain magnetic resonance imaging studies suggest volume loss in the mesial temporal lobe and limbic regions in subjects with Parkinson's disease with visual hallucinations, relative to those without visual hallucinations. However, these studies have not always controlled for the presence of cognitive impairment or dementia, which are common co-morbidities of hallucinations in Parkinson's disease and whose neuroanatomical substrates may involve mesial temporal lobe and limbic regions. Therefore, we used structural magnetic resonance imaging to examine grey matter atrophy patterns associated with visual hallucinations, comparing Parkinson's disease hallucinators to Parkinson's disease non-hallucinators of comparable cognitive function. We studied 50 subjects with Parkinson's disease: 25 classified as current and chronic visual hallucinators and 25 as non-hallucinators, who were matched for cognitive status (demented or non-demented) and age (± 3 years). Subjects underwent (i) clinical evaluations; and (ii) brain MRI scans analysed using whole-brain voxel-based morphometry techniques. Clinically, the Parkinson's disease hallucinators did not differ in their cognitive classification or performance in any of the five assessed cognitive domains, compared with the non-hallucinators. The Parkinson's disease groups also did not differ significantly in age, motor severity, medication use or duration of disease. On imaging analyses, the hallucinators, all of whom experienced visual hallucinations, exhibited grey matter atrophy with significant voxel-wise differences in the cuneus, lingual and fusiform gyri, middle occipital lobe, inferior parietal lobule, and also cingulate, paracentral, and precentral gyri, compared with the non-hallucinators. Grey matter atrophy in the hallucinators occurred predominantly in brain regions responsible for processing visuoperceptual information including the ventral 'what' and dorsal 'where' pathways, which are important in object and facial recognition and identification of spatial locations of objects, respectively. Furthermore, the structural brain changes seen on magnetic resonance imaging occurred independently of cognitive function and age. Our findings suggest that when hallucinators and non-hallucinators are similar in their cognitive performance, the neural networks involving visuoperceptual pathways, rather than the mesial temporal lobe regions, distinctively contribute to the pathophysiology of visual hallucinations and may explain their predominantly visual nature in Parkinson's disease. Identification of distinct structural MRI differences associated with hallucinations in Parkinson's disease may permit earlier detection of at-risk patients and ultimately, development of therapies specifically targeting hallucinations and visuoperceptive functions.

Keywords: dementia; hallucinations; magnetic resonance imaging; Parkinson's disease; voxel-based morphometry

Abbreviation: MDS-UPDRS = Movement Disorder Society Unified Parkinson's Disease Rating Scale

Introduction

Psychosis in Parkinson's disease clinically ranges from illusions to hallucinations and delusions, with visual hallucinations being the most frequent form (Fenelon *et al.*, 2000; Ravina *et al.*, 2007; Goetz *et al.*, 2011). Visual hallucinations develop in >50% of patients with Parkinson's disease and once present, are progressive, chronic (Hely *et al.*, 2005; Forsaa *et al.*, 2010) and associated with increased nursing home placement, morbidity and mortality (Goetz and Stebbins, 1995; Aarsland *et al.*, 2000). Risk factors for hallucinations in patients with Parkinson's disease include older age, advanced disease, cognitive impairment, depression and sleep disturbances (Fenelon *et al.*, 2000). Although dopaminergic medications play a role in the pathophysiology of Parkinson's disease hallucinations, the development of the hallucinations extends beyond mesolimbic dopaminergic receptor hypersensitivity or stimulation. At present, however, their exact mechanisms and neurobiological substrates are not fully known. Current evidence favours multiple levels of cerebral dysfunction including aberrant 'bottom-up' and 'top-down' visual processing, with faulty input from the visual system and brainstem to higher cortical visual areas (e.g. occipital-temporal and occipital-parietal lobes) and altered cortical integration from orbitofrontal and dorsolateral prefrontal cortex to cortical visual regions (Ffytche and Howard, 1999; Collerton *et al.*, 2005; Shine *et al.*, 2011; Onofrj *et al.*, 2012). Furthermore, these visual processing aberrations invoke the ventral 'what' and dorsal 'where' streams, which are responsible for object recognition and spatial location, respectively (Ungerleider and Mishkin, 1982; Goodale and Milner, 1992). Visual hallucinations experienced by patients with Parkinson's disease may reflect disturbances in the brain's ability to attend to and process these visual stimuli, integrate sensory information and prior expectations, and generate correct interpretations of visual input, thereby integrating elements of attentional, cognitive, emotional and visuoperceptive processes (Diederich *et al.*, 2005; Shine *et al.*, 2011; Onofrj *et al.*, 2012).

Neuroimaging studies using structural, metabolic and functional techniques permit *in vivo* investigations of underlying brain abnormalities in patients with Parkinson's disease with hallucinations. Metabolic and functional neuroimaging studies in Parkinson's disease visual hallucinators compared with non-hallucinators frequently reveal dysfunction in brain regions involved in visuoperception, namely the occipital, temporal and parietal lobes, and thus suggest that the culprit may be primarily aberrant visual processing (Okada *et al.*, 1999; Stebbins *et al.*, 2004; Oishi *et al.*, 2005; Matsui *et al.*, 2006; Boecker *et al.*, 2007; Meppelink *et al.*, 2009). This decreased activation in the visual 'what' and 'where' regions of the brain in hallucinators has been coupled in some studies with increased activation of frontal or subcortical regions in response to functional MRI visual stimulation paradigms (Stebbins *et al.*, 2004) or hyperperfusion of temporal, precentral (Oishi *et al.*, 2005) or frontal regions (Boecker *et al.*, 2007) on metabolic imaging studies. Other functional magnetic resonance imaging (MRI) studies, however, reveal

decreased activation in frontal regions in hallucinators just before image recognition (Meppelink *et al.*, 2009) or decreased activation in fronto-parietal networks (Shine *et al.*, 2013). Although these somewhat differing results of metabolic and functional neuroimaging studies do not resolve the debate of bottom-up or top-down processing, they are united by the shared theme of disrupted posterior and anterior brain regions. Collectively, they suggest a role of attentional, cognitive, emotional, and visuoperceptive processes, individually or in combination, in the clinical manifestation of visual hallucinations.

Despite the predominant decreased activation in the posterior visuoperceptive brain regions found in many of the metabolic and functional neuroimaging studies, it is surprising that, to date, only one structural brain MRI study using an automated, unbiased analytic technique of whole brain voxel-based morphometry to compare Parkinson's disease visual hallucinators to non-hallucinators has revealed grey matter atrophy in these areas (i.e. lingual gyrus, superior parietal lobule) (Ramirez-Ruiz *et al.*, 2007). Most other structural MRI studies using voxel-based morphometry analyses demonstrate predominantly decreased grey matter volumes in hippocampal, limbic, paralimbic and neocortical regions in Parkinson's disease hallucinators, compared with non-hallucinators (Ibarretxe-Bilbao *et al.*, 2008, 2010; Shin *et al.*, 2012; Shine *et al.*, 2013). These brain regions, particularly the mesial temporal lobe, however, are also implicated in memory and cognitive functions (Squire and Zola-Morgan, 1991) and exhibit atrophy on structural MRI scans in patients with Parkinson's disease dementia (Duncan *et al.*, 2013). Thus, the co-occurrence of cognitive impairment or dementia in Parkinson's disease hallucinators potentially confounds our interpretation of these MRI findings as representing neuroanatomical substrates specifically associated with hallucinations in Parkinson's disease. Moreover, in several MRI studies, even those hallucinating patients with Parkinson's disease classified as 'non-demented' frequently exhibited significantly worse performance on global cognitive function, memory, and executive function tests, compared to non-demented patients with Parkinson's disease without hallucinations (Ibarretxe-Bilbao *et al.*, 2008; Shin *et al.*, 2012), thereby indicating that the examined groups were not truly of comparable cognitive abilities.

Although the pathophysiology of hallucinations may be linked to impaired attentional and visuoperceptive processing, and although their presence has been considered an important predictor of dementia (Aarsland *et al.*, 2003), we hypothesize that these two behavioural abnormalities, namely hallucinations and dementia, may have distinct and independent neurobiological substrates. The identification of structural MRI differences in Parkinson's disease hallucinators, independent of cognitive deficits, would be clinically important not only for more accurate establishment of underlying neurobiological mechanisms, but also for the development of novel therapies targeting Parkinson's disease hallucinations and visuoperceptive functions. As such, it is important to examine Parkinson's disease hallucinators and non-hallucinators of comparable cognitive function to identify neuroanatomical

contributions that are specific to Parkinson's disease hallucinations. Accordingly, the aim of our study was to use structural MRI whole-brain voxel-based morphometry analyses to identify changes in grey matter in subjects with Parkinson's disease with current and chronic visual hallucinations where dementia was controlled for, that is, where subjects were matched for cognitive status (demented/non-demented) to subjects with Parkinson's disease without visual hallucinations.

Materials and methods

Subjects

Subjects with Parkinson's disease were recruited from the Rush University Movement Disorder clinic as part of an ongoing study of clinical and neuroimaging markers of Parkinson's disease-related cognitive and behavioural problems (Goldman *et al.*, 2013). From a cohort of 100 subjects with Parkinson's disease, we identified 25 with current and chronic visual hallucinations. From the remaining 75 non-hallucinators, we selected 25 who were matched to the hallucinator group on cognitive status and age. All subjects with Parkinson's disease were examined by a movement disorders neurologist (J.G.G.) and met UK Parkinson's disease Society Brain Bank criteria (Hughes *et al.*, 1993). Subjects with Parkinson's disease had disease durations of ≥ 4 years and were on stable medication regimens. Exclusionary criteria were: (i) atypical or secondary forms of parkinsonism (e.g. dementia with Lewy bodies, multiple system atrophy, progressive supranuclear palsy, corticobasal degeneration, or parkinsonism due to neuroleptic exposure, cerebrovascular disease, or known structural causes); (ii) severe or unstable depression; (iii) anticholinergic medications (e.g. trihexyphenidyl, benztropine, tricyclic antidepressants); (iv) other medical or neurological reasons for cognitive impairment (e.g. seizures, strokes, head trauma, significant vision or hearing deficits); or (v) contraindications to MRI (e.g. cardiac pacemaker/defibrillator, surgical clips, foreign metallic implants). In subjects with Parkinson's disease with dementia, all had motor symptoms for at least 1 year before dementia onset. The study was approved by the Institutional Review Board of Rush University in Chicago, IL; subjects gave written informed consent to participate in the study.

Subjects with Parkinson's disease were classified as current and chronic hallucinators if they met the following criteria:

- (i) current hallucinations: a score ≥ 1 on the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part I question 1.2 'Hallucinations and Psychosis' (Goetz *et al.*, 2008), which determines whether the patient has seen, heard, smelled or felt things that were not really there over the past week. The question is scored as follows: 0, normal, no hallucinations or psychotic behaviour; 1, slight, illusions or non-formed hallucinations, but patient recognizes them without loss of insight; 2, mild, formed hallucinations independent of environmental stimuli, no loss of insight; 3, moderate, formed hallucinations with loss of insight; 4, severe, patient has delusions or paranoia; and
- (ii) chronic hallucinations: the presence of psychotic symptoms, occurring for at least 1 month, and fulfilling diagnostic criteria for Parkinson's disease-associated psychosis proposed by the National Institute of Health/National Institute of Mental Health (NIH/NIMH) Work Group (Ravina *et al.*, 2007).

All Parkinson's disease hallucinators had visual hallucinations, though subjects with hallucinations in other sensory modalities (e.g. auditory,

olfactory, tactile) were included in this group if these hallucinations occurred in addition to visual hallucinations. Subjects with Parkinson's disease without hallucinations had a score of 0 ('normal') on the MDS-UPDRS Hallucinations and Psychosis question and did not meet the NIH/NIMH Work Group criteria for Parkinson's disease-associated psychosis.

The subjects with Parkinson's disease were matched by their cognitive status, defined as either demented or non-demented, so that the hallucinator and non-hallucinator groups had equal numbers of demented subjects. Dementia was defined by MDS Parkinson's disease dementia criteria (Emre *et al.*, 2007) and determined in a consensus conference involving a neurologist specializing in movement disorders and neuropsychiatry (J.G.G.) and two senior neuropsychologists (G.T.S., B.B.), using the clinical and neuropsychological data described below and previously published methods (Goldman *et al.*, 2013). The Parkinson's disease subject groups were also matched by age (± 3 years).

Evaluations

Clinical evaluations included assessments of demographics, medications and disease-related features including the MDS-UPDRS and Hoehn and Yahr stage (Goetz *et al.*, 2008). Dopaminergic medications for Parkinson's disease were converted to levodopa equivalent daily doses (Tomlinson *et al.*, 2010). Antipsychotic medications were converted to chlorpromazine equivalents (Woods, 2003). Subjects with Parkinson's disease underwent comprehensive cognitive evaluations including: (i) Mini-Mental State Examination (Folstein *et al.*, 1975); (ii) Clinical Dementia Rating scale (Morris, 1993); and (iii) individual neuropsychological tests representing five cognitive domains (attention/working memory, executive function, language, declarative memory, and visuospatial function) as recommended by a Movement Disorder Society Task Force (Litvan *et al.*, 2012), which were used to determine cognitive status. The neuropsychological battery included the following: (i) attention and working memory [Digit Span Backwards and Letter Number Sequencing from the Wechsler Adult Intelligence Scale-III (WAIS-III), Trail making Test-A], (ii) executive function (Controlled Oral Word Association Test, Goodglass and Kaplan Clock Drawing Test; (iii) language (Boston Naming Test, WAIS-III Similarities); (iv) memory (three trials of word list learning and delayed recall from the Consortium to Establish a Registry for Alzheimer's disease, Logical Memory I and II prose passages); and (v) visuospatial function (Benton Judgment of Line Orientation, Goodglass and Kaplan Clock Copying Test). Raw scores for neuropsychological tests were transformed to z-scores based upon normative data from healthy, cognitively normal controls at our centre (Goldman *et al.*, 2012). Cognitive domain scores were calculated by averaging z-scores for neuropsychological tests within specific domains.

Magnetic resonance imaging acquisition and processing

Magnetic resonance images were acquired on a 1.5 T General Electric Signa scanner. Subjects underwent a 3D MRI with a T₁-weighted MPRAGE sequence with the following parameters: 166 contiguous sagittal images, 1.2 mm thick, matrix = 192 × 192, field of view = 24 cm, echo time = minimum full, repetition time = 1000 ms, flip angle = 8°, NEX (average) 1, phase field of view 1, and band width 15.63 Hz (Jack *et al.*, 2010).

Structural imaging data were preprocessed and analysed using statistical parametric mapping 8 (SPM8) (<http://www.fil.ion.ucl.ac.uk/spm>) implemented in Matlab 7.4a (MathWorks). The VBM8 toolbox

was used to perform the following steps on the raw images: segmentation into grey matter, white matter, and cerebrospinal fluid based on tissue probability maps; and using DARTEL processing techniques, which provide an algorithm for accurate diffeomorphic image registration, normalization of grey matter segments to a grey matter template in Montreal Neurological Institute (MNI) space; modulation of the normalized grey matter images with the Jacobian determinants; and smoothing of images with a 3D Gaussian filter of 8 mm full-width at half-maximum (Good *et al.*, 2001; Ashburner, 2007). An estimation of total intracranial volume was calculated from the addition of global grey, white, and CSF volume carried out by SPM8 as part of the standard processing stream and was included as a covariate in the analysis of covariance when comparing grey matter volumes between the Parkinson's disease hallucinator and non-hallucinator groups. Voxels that demonstrated significant group differences between Parkinson's disease hallucinators and non-hallucinators were used to create regions of interest and extract volume measurements using the statistical parametric mapping sample volume function. Multiple linear regression models were used to examine the relationship between the grey matter volumes for these regions (i.e. independent variable) and severity of hallucinations as measured by the MDS-UPDRS Part I question 1.2. Neuroanatomical regions of significance were identified with the SPM glassbrain32 program, which names the MNI coordinates used in statistical parametric mapping and adds corresponding Talairach coordinates based on the Wake Forest University PickAtlas database (www.fmri.whubmc.edu). Corresponding Brodmann areas for neuroanatomical regions of significance were identified using Talairach Daemon (www.talairach.org). All MRI processing and analyses were performed blinded to subject identity and clinical diagnosis.

Statistical analyses

Statistical analyses for demographic and disease-related variables were performed with SPSS 18.0 for Mac (PASW 19; SPSS Inc.)

using two-tailed *t*-tests or Chi-square tests as appropriate. Statistical significance for these analyses was set at $P < 0.05$. For image analyses, between-group voxel-wise comparisons were conducted with the general linear model within SPM8. Group differences were tested using a whole-brain approach. The significance threshold for differences on image analyses was set at $P < 0.01$, uncorrected, with a cluster extent threshold, $k = 10$. Relationships between grey matter volumes extracted from the regions that significantly differed between groups and the hallucination severity, as measured by the MDS-UPDRS 'Hallucinations and Psychosis' item were examined in the Parkinson's disease hallucinators using the SPM8 multiple regression (correlation) module with the same statistical and cluster thresholds as the whole-brain analysis.

Results

Clinical characteristics

Twenty-five subjects with Parkinson's disease with current and chronic hallucinations were compared to 25 subjects with Parkinson's disease without hallucinations. All hallucinators had visual hallucinations as their primary modality; additional auditory hallucinations were present in 6/25 hallucinators. Of the hallucinations, the median score for the MDS-UPDRS question on hallucinations and psychosis was 2 (range 1–4) with 10 subjects (40%) with illusions or non-formed hallucinations (score 1), 11 subjects (44%) with mild, formed hallucinations with insight (score 2), two subjects (8%) with moderate, formed hallucinations without insight (score 3), and two subjects (8%) with delusions (score 4). There were no significant differences between the hallucinator and non-hallucinator subjects in age, gender, education or duration of Parkinson's disease (Table 1). The two Parkinson's disease groups were matched in terms

Table 1 Clinical features of the Parkinson's disease cohort

	Parkinson's disease non-hallucinators (n = 25)	Parkinson's disease hallucinators (n = 25)	P-value
Demographics			
Age, years	75.4 (6.1)	74.8 (6.0)	0.73
Male, n (%)	18 (51.4)	17 (48.6)	0.76
Education, years	15.7 (2.9)	15.4 (3.3)	0.75
Disease duration, years	10.8 (4.4)	13.1 (4.6)	0.08
Cognition			
MMSE	25.1 (4.4)	23.9 (5.4)	0.38
CDR Global Score, median (range)	0.5 (0–2)	0.5 (0–2)	0.46
CDR Sum of Boxes	3.2 (3.2)	3.5 (3.1)	0.72
Motor			
MDS-UPDRS total motor score	43.5 (13.2)	39.0 (13.8)	0.24
MDS-UPDRS Hoehn and Yahr, median (range)	3 (2–5)	3 (2–5)	0.85
Medications			
LEDD, mg/d	787.8 (356.9)	808.3 (329.5)	0.83
Dopamine agonist use, n (%)	7 (14)	8 (16)	0.76
Antipsychotic use, n (%)	3 (12.0)	6 (24.0)	0.27
CPZ equivalent dose, mg/d	12.0 (37.1)	13.3 (27.6)	0.33
Cognitive medication, n (%)	7 (28.0)	7 (28.0)	1.0

Data presented as mean (\pm SD) unless otherwise noted.

CDR = Clinical Dementia Rating; CPZ = chlorpromazine; LEDD = levodopa equivalent daily dose; MMSE: Mini-Mental State Examination.

Table 2 Cognitive domain z-scores in the Parkinson's disease cohort

	Parkinson's disease non-hallucinators (n = 25)	Parkinson's disease hallucinators (n = 25)	P-value
Attention/working memory	-2.13 (1.6)	-2.01 (1.5)	0.78
Executive function	-2.2 (1.2)	-2.0 (1.3)	0.55
Language	-1.2 (1.4)	-1.1 (1.3)	0.80
Memory	-2.2 (1.4)	-1.8 (1.5)	0.37
Visuospatial function	-2.1 (2.0)	-2.8 (1.9)	0.19

Data presented as mean (SD).

of their cognitive status with 12 demented and 13 non-demented subjects per group. There were no significant differences between the hallucinator and non-hallucinator groups in global cognitive measures, namely mean Mini-Mental State Examination scores, Clinical Dementia Rating global scores, or Clinical Dementia Rating sum of boxes scores. Also, the groups did not significantly differ in their performance across the five cognitive domains, depicted as mean z-scores of neuropsychological tests in the domains of attention/working memory, executive function, language, memory, and visuospatial functions (Table 2). Finally, the Parkinson's disease groups did not differ significantly in motor severity scores, measured by the MDS-UPDRS part III motor score and Hoehn and Yahr stage, or dopaminergic medications for Parkinson's disease, including levodopa equivalent doses and use of dopamine agonists. Cognitive medications (i.e. cholinesterase inhibitors or memantine) were used by seven subjects in each Parkinson's disease group. Antipsychotic medications (i.e. quetiapine) were used by six hallucinators and three non-hallucinators; the non-hallucinators, however, were taking low dose quetiapine for problems with sleep and impulsivity rather than hallucinations.

Image analyses

On whole-brain voxel-based morphometry analyses, the Parkinson's disease hallucinators exhibited significant clusters of reduced grey matter volume compared to the non-hallucinators. The regions where the hallucinators exhibited reduced grey matter volumes included the bilateral cuneus, fusiform, middle occipital, precentral, and cingulate gyri and inferior parietal lobules; right lingual gyrus, and left paracentral gyrus (Fig. 1 and Table 3). We did not detect any grey matter volume differences between the two groups in the mesial temporal lobe, insula, or brainstem, which were regions specifically examined given findings in previous studies. There were no cerebral areas where the non-hallucinators had significantly greater grey matter volume loss than hallucinators.

There was a significant relationship between the grey matter volumes, calculated for those regions in which the hallucinating subjects demonstrated reduced grey matter, and the severity of hallucinations, measured by the MDS-UPDRS 'Hallucinations and Psychosis' item. Four of the 18 regions that had reduced grey matter volumes on voxel-based morphometry analysis in the hallucinating patients significantly contributed to the regression

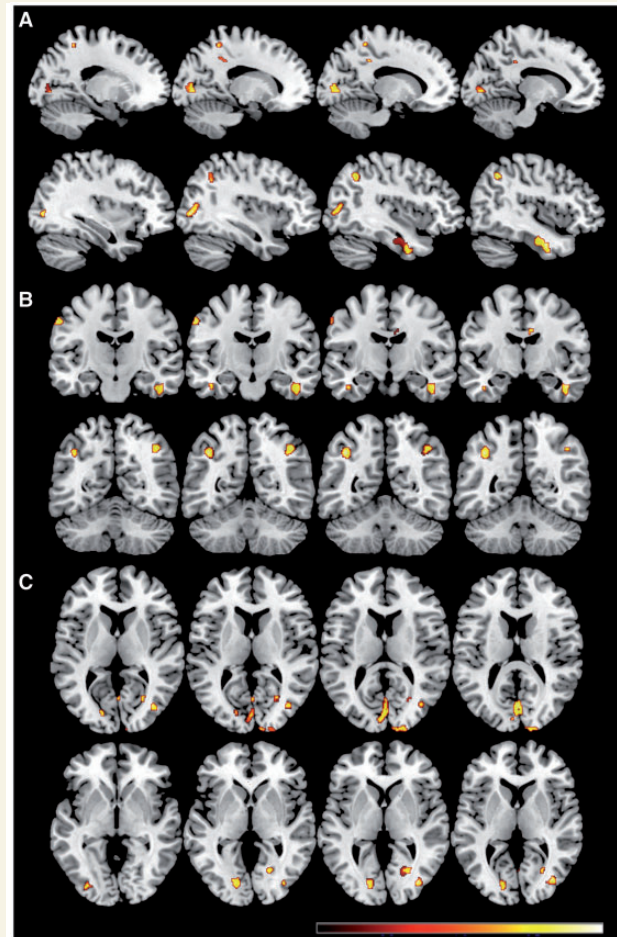


Figure 1 Location of significant clusters of grey matter volume loss in subjects with Parkinson's disease with hallucinations compared with subjects with Parkinson's disease without hallucinations. Results overlapped on a T₁-weighted image of healthy, control brain. Yellow colour indicates significantly different areas involving cuneus, fusiform, lingual, middle occipital and cingulate gyri, inferior parietal lobules, and precentral gyrus (A, sagittal; B, coronal; C, axial slices), ($P < 0.01$, uncorrected).

model ($P = 0.027$): left inferior parietal lobule, left cuneus, right lingual gyrus, and right precentral gyrus (Table 4).

To explore further the potential dissociation of neuroanatomical regions involved in hallucinations and dementia, we compared subjects with Parkinson's disease with and without dementia, controlling for hallucination status, on whole-brain voxel-based morphometry analyses using a 2 (demented versus non-demented) \times 2 (hallucinator versus non-hallucinator) factorial design (Fig. 2 and Table 5). In this analysis, demented subjects had significantly reduced grey matter volumes in predominantly frontal and temporal regions, including bilateral parahippocampal gyri; inferior frontal, medial frontal, and middle frontal gyri; superior temporal gyri; and insula; right uncus, amygdala; and left claustrum and hippocampus, compared with non-demented subjects ($P < 0.01$ uncorrected, $k = 10$). However, we did not detect grey matter atrophy in the occipital-temporal-parietal regions

Table 3 Anatomical location of areas showing significant differences in grey matter volume between Parkinson's disease subjects with and without hallucinations

Region	Cluster size (mm ³)	Cluster significance	T-value	Z-value	Talairach coordinates (x, y, z)
Right cuneus (BA 18)	482	0.001	3.16	2.99	1, -72, 19
Right fusiform gyrus (BA 20)	335	0.001	3.43	3.23	43, -5, -22
Left inferior parietal lobule (BA 40)	187	0.001	3.37	3.17	-39, -51, 38
Left precentral gyrus (BA 6)	169	0.001	3.21	3.04	-61, -11, 39
Right middle occipital gyrus (BA 18)	140	0.005	2.68	2.58	9, -97, 15
Right middle occipital gyrus (BA 19)	140	0.001	3.46	3.25	36, -75, 7
Left cuneus (BA 17)	139	0.002	3.07	2.92	-18, -78, 5
Right lingual gyrus (BA 19)	113	0.003	2.94	2.8	19, -64, 3
Right inferior parietal lobule (BA 40)	105	0.001	3.15	2.98	40, -53, 43
Right cingulate gyrus (BA 24)	89	0.001	3.54	3.32	9, 0, 29
Left/right cingulate gyrus (BA 24)	53	0.002	3.07	2.92	0, 5, 40
Left fusiform/subgyral gyrus (BA 20)	39	0.003	2.87	2.74	-43, -13, -20
Left paracentral lobule (BA 5)	38	0.006	2.64	2.53	-16, -42, 55
Left middle occipital gyrus (BA 18)	37	0.001	3.03	3.03	-30, -80, 1
Left cingulate gyrus (BA 31)	23	0.003	2.92	2.78	-15, -36, 36
Left middle occipital gyrus (BA 19)	21	0.006	2.64	2.54	-52, -78, 5
Right precentral gyrus (BA 6)	18	0.004	2.73	2.62	65, 6, 19
Right lingual gyrus (BA 18)	17	0.007	2.55	2.46	6, -83, -5

BA = Brodmann area.

Table 4 Anatomical location of areas showing a significant relationship to hallucination severity

Region	Cluster size (mm ³)	Cluster significance	T-value	Z-value	Talairach coordinates (x, y, z)
Left inferior parietal lobule (BA 40)	62	0.001	4.11	3.52	-37, -53, 44
Left cuneus (BA 18)	22	0.001	3.56	3.15	-4, -82, 17
Right lingual gyrus (BA 19)	22	0.003	3.08	2.79	18, -68, 5
Right precentral gyrus (BA 6)	15	0.001	3.41	3.04	64, 4, 22

BA = Brodmann area.

that are typically associated with visuoperceptive functions and were found in our hallucinator versus non-hallucinator comparison.

Discussion

Our study has several key findings. Compared with patients with Parkinson's disease without hallucinations, those with current and chronic visual hallucinations exhibit reduced grey matter volume on structural brain MRI in regions specifically associated with visuoperceptual function, independent of cognitive status. These regions of grey matter atrophy in the hallucinators correspond selectively and neuroanatomically to brain areas associated with visuoperceptual processing and include the ventral 'what' and dorsal 'where' visual streams. These regions, frequently implicated in theories of visual hallucinations in Parkinson's disease (discussed below), have been shown to exhibit decreased perfusion or activation in metabolic or functional neuroimaging studies of patients with Parkinson's disease with hallucinations, but have not previously demonstrated atrophy in most structural MRI studies, possibly because of confounds of co-morbid cognitive impairment. In

contrast with several structural MRI studies, we did not detect grey matter volume loss in the hallucinators in brain regions that are frequently associated with cognitive impairment and dementia in Parkinson's disease such as mesial temporal, insular, limbic, or frontal lobe regions. Conversely, when controlling for hallucinations, we demonstrated atrophy in these frontal, insular, limbic, and temporal regions in demented subjects with Parkinson's disease, but not in the posterior occipital-temporal-parietal regions. Thus, our structural MRI findings of highly localized structural brain abnormalities in the visuoperceptive system and the fact that the hallucinations experienced by subjects with Parkinson's disease are predominantly visual ones suggest that specific brain and behaviour relationships underlie hallucinations in Parkinson's disease. Our findings also suggest that the neuroanatomical substrates involved in visual hallucinations in Parkinson's disease are distinct from those typically found on structural MRI analyses in cognitive impairment or dementia in Parkinson's disease, a dissociation that has not previously been shown.

The grey matter atrophy in the Parkinson's disease hallucinator subjects found in our study is of particular interest in terms of clinico-anatomical correlations, because the affected regions play essential roles in primary and secondary visual processing and

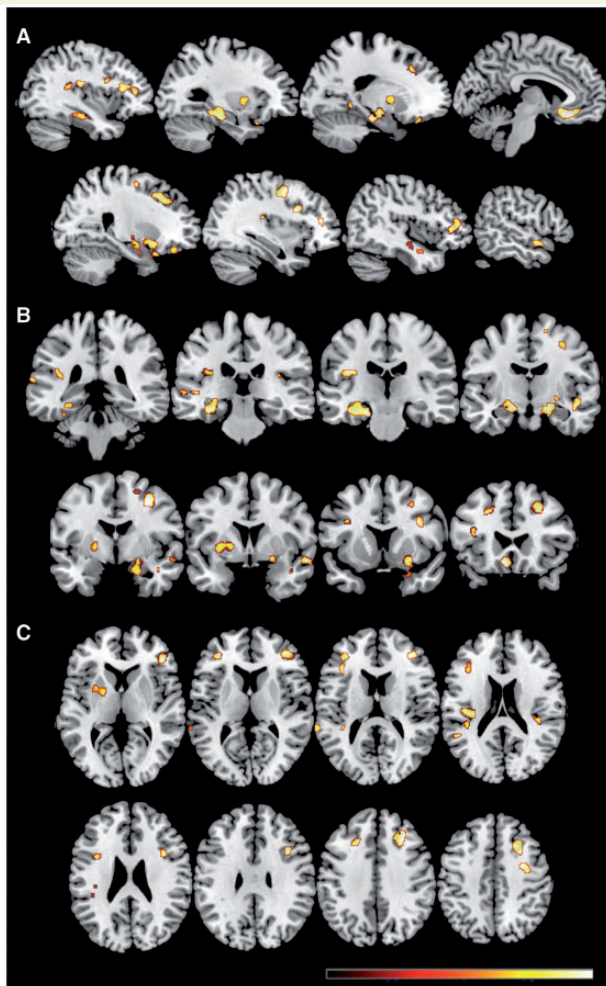


Figure 2 Location of significant clusters of grey matter volume loss in subjects with Parkinson's disease with dementia compared with subjects with Parkinson's disease without dementia. Results overlapped on a T₁-weighted image of healthy, control brain. Yellow colour indicates significantly different areas involving inferior frontal, medial frontal, and middle frontal and superior temporal gyri; parahippocampal gyrus; hippocampus; amygdala; insula; uncus; and claustrum (A, sagittal; B, coronal; C, axial slices), ($P < 0.01$, uncorrected).

visuoperceptual functions (Ungerleider and Mishkin, 1982). Specifically, the brain regions exhibiting atrophy selectively involve (i) areas responsible for determining patterns, light intensity, colours, shapes, words, visual memory, and primary visual processing (i.e. the middle occipital gyrus, lingual gyrus, and cuneus); (ii) areas responsible for recognizing faces and body regions (i.e. the fusiform gyrus which forms part of the visuoperceptive ventral 'what' stream); and (iii) areas responsible for multi-modal processing and network connections among areas involved in motor, sensory, emotional, language, cognitive, attentional, and visuo-spatial functions (i.e. inferior parietal lobule and cingulate gyrus). These clinico-anatomical correlations may even help explain why the majority of hallucinations in Parkinson's disease are visual ones, manifesting as misperceptions of still or moving objects, or

as hallucinations of altered faces or figures, and frequently invoking heightened emotions (Fenelon *et al.*, 2000; Goetz *et al.*, 2011). Furthermore, it is interesting to note that similar clinico-anatomical correlates have been detected in voxel-based morphometry studies of schizophrenia. For example, subjects with schizophrenia experiencing auditory verbal hallucinations demonstrate reduced grey matter volume in the bilateral superior temporal gyrus including Heschl's gyri (Modinos *et al.*, 2013), an area involved in auditory processing. These findings of brain-behaviour correlates in schizophrenic subjects, as well as in our study of Parkinson's disease hallucinators, support a model of aberrant neural system processing at different levels of sensory processing.

Our findings of grey matter atrophy in predominantly visuoperceptive regions in the hallucinating subjects with Parkinson's disease differ from findings of several other structural MRI studies in which the Parkinson's disease hallucinators exhibited primarily hippocampal or temporal (Ibarretxe-Bilbao *et al.*, 2008, 2010; Shin *et al.*, 2012), insular (Shine *et al.*, 2013), frontal (Ibarretxe-Bilbao *et al.*, 2010; Sanchez-Castaneda *et al.*, 2010; Shin *et al.*, 2012), thalamic or pedunculopontine atrophy (Shin *et al.*, 2012; Janzen *et al.*, 2012), compared to Parkinson's disease non-hallucinators. Several differences in clinical and imaging methodologies between those studies and ours could account for these differences. One key difference is our careful control of cognitive abilities when comparing Parkinson's disease hallucinators and non-hallucinators. The two groups in our study had comparable numbers of demented and non-demented subjects in each group and did not differ significantly on scores of the five cognitive domains tested. In several other studies, in contrast, the Parkinson's disease hallucinators had greater cognitive impairment than the non-hallucinators. In addition, studies have varied with regard to the definitions of Parkinson's disease dementia [e.g. Mini-Mental State Examination scores < 24 , Diagnostic Statistical Manual (DSM) IV-TR or MDS Parkinson's disease dementia criteria] (American Psychiatric Association, 2000; Ibarretxe-Bilbao *et al.*, 2008; Janzen *et al.*, 2012; Shin *et al.*, 2012) that were used as either criteria to include subjects, or to exclude subjects if the study focused on non-demented subjects with Parkinson's disease. The tendency towards worse cognitive function in subjects with Parkinson's disease with hallucinations could lead to greater detection of atrophy on structural MRI in mesial temporal lobe, limbic and neocortical regions. Grey matter atrophy in these areas has been detected in patients with Parkinson's disease with cognitive impairment and dementia in several structural MRI studies (Duncan *et al.*, 2013). Furthermore, greater amnesic deficits in those hallucinating subjects with Parkinson's disease classified as demented by DSM IV-TR criteria, which require memory impairment by definition, could also contribute to grey matter atrophy in the mesial temporal lobe on MRI, an area implicated in declarative memory function (Squire and Zola-Morgan, 1991). Even when Parkinson's disease hallucinators were considered non-demented in many of these studies, they performed worse on tests of global cognitive function and on multiple cognitive domains compared to Parkinson's disease non-hallucinators. The hallucinators had worse scores on: (i) the Mini-Mental State Examination (Ramirez-Ruiz *et al.*, 2007; Ibarretxe-Bilbao *et al.*, 2008); (ii) memory on verbal list learning and recall tests (Ramirez-Ruiz *et al.*, 2007; Ibarretxe-Bilbao *et al.*,

Table 5 Anatomical location of areas showing significant differences in grey matter volume between demented and non-demented subjects with Parkinson's disease

Region	Cluster size (mm ³)	Cluster significance	T-value	Z-value	Talairach coordinates (x, y, z)
Left parahippocampal gyrus, hippocampus (BA 35, 28)	1222	0.001	3.41	3.2	−19, −21, −15
Right inferior frontal gyrus, parahippocampal gyrus, amygdala (BA 47)	1038	0.001	3.46	3.24	25, 15, −23
Right middle frontal gyrus (BA 8, 9)	503	0.001	3.33	3.13	28, 31, 34
Left medial frontal gyrus (BA 11)	469	0.001	3.6	3.35	−7, 27, −13
Right middle frontal gyrus (BA 6, 10)	376	0.001	3.51	3.28	36, 40, 12
Right middle frontal gyrus (BA 6)	341	0.001	3.75	3.47	31, 1, 44
Left claustrum	260	0.005	2.72	2.6	−31, 3, 1
Left middle frontal gyrus (BA 10, 46)	255	0.001	3.38	3.17	−34, 40, 9
Right medial frontal gyrus (BA 11)	234	0.001	3.16	2.98	1, 57, −18
Right superior temporal lobe (BA 21)	178	0.003	2.95	2.81	56, 2, −10
Left insula (BA 13)	166	0.001	3.23	3.04	−37, −21, 22
Right inferior frontal gyrus (BA 9)	130	0.001	3.2	3.02	34, 11, 23
Right inferior frontal gyrus (BA 6)	111	0.001	3.44	3.22	19, −2, 54
Right temporal gyrus (BA 21)	109	0.003	2.9	2.76	46, −11, −8
Left medial frontal gyrus (BA 9)	105	0.001	3.69	3.42	−21, 26, 30
Right inferior frontal gyrus (BA 11)	103	0.005	2.72	2.6	24, 36, −18
Left superior temporal gyrus (BA 22)	76	0.002	3.04	2.88	−67, −37, 14
Left insula (BA 13)	70	0.005	2.71	2.59	−40, −32, 21
Left inferior frontal gyrus (BA 47)	66	0.004	2.75	2.63	−21, 31, −22
Right insula (BA 13)	60	0.005	2.7	2.58	39, −28, 19
Left superior temporal gyrus (BA 13)	54	0.001	3.12	2.95	−50, −46, 20
Left parahippocampal gyrus (BA 19)	53	0.004	2.78	2.65	−19, −44, −2
Left inferior frontal gyrus (BA 9)	48	0.003	2.9	2.75	−36, 10, 23
Left superior temporal gyrus (BA 22)	41	0.006	2.64	2.53	−59, −26, 3
Right uncus (BA 28)	35	0.005	2.66	2.55	22, −15, −35
Left superior temporal gyrus (BA 22)	29	0.006	2.64	2.53	−48, −26, 3
Right superior temporal gyrus (BA 38)	21	0.006	2.61	2.5	42, −1, −18
Left inferior frontal gyrus (BA 47)	20	0.008	2.49	2.4	−31, 18, −21

BA = Brodmann area.

2008); (iii) visual memory (Shin *et al.*, 2012); (iv) attention and executive function on tests of fluency, set shifting, and interference (Ibarretxe-Bilbao *et al.*, 2010; Shin *et al.*, 2012; Shine *et al.*, 2013); and (v) visuospatial function with facial recognition tasks (Ramirez-Ruiz *et al.*, 2007; Ibarretxe-Bilbao *et al.*, 2010). Other important differences among structural MRI studies include various definitions of visual hallucinations (e.g. frequency, severity, and/or rating scales used), sample sizes (e.g. ranging from 8–46 Parkinson's disease hallucinators in studies), and imaging methods (e.g. MRI scanners, statistical parametric mapping versions, whole brain voxel-based morphometry or selective region of interest approaches, choices in smoothing kernels, cluster threshold significance, and corrections for multiple comparisons used). An additional consideration is that in other studies, the Parkinson's disease hallucinators compared with the non-hallucinators had worse motor impairment (Ramirez-Ruiz *et al.*, 2007; Ibarretxe-Bilbao *et al.*, 2008; Janzen *et al.*, 2012), longer disease duration (Sanchez-Castaneda *et al.*, 2010; Janzen *et al.*, 2012) and greater depressed mood on standard rating scales (Ramirez-Ruiz *et al.*, 2007; Ibarretxe-Bilbao *et al.*, 2008). Our matching for cognitive status and age, along with the lack of significant between-group differences in Parkinson's disease duration, motor severity, or

depression, in the hallucinators and non-hallucinators represents a major strength of our study and thus, allows for the first time a clinico-anatomical analysis that separates the regions associated with hallucinations from those associated with dementia as two distinct, but sometimes overlapping, clinical problems.

To the best of our knowledge, only one other structural MRI study has detected greater grey matter atrophy in regions associated with visual processing in Parkinson's disease hallucinators compared with non-hallucinators (Ramirez-Ruiz *et al.*, 2007). Our findings further extend this work, which demonstrated grey matter atrophy in three regions, the left lingual gyrus and bilateral superior parietal lobes in Parkinson's disease hallucinator subjects. The structural MRI findings of grey matter atrophy in visuoceptive regions in Parkinson's disease hallucinators complement previous metabolic and functional neuroimaging studies, which reveal that similar regions are affected. These studies show decreased cerebral perfusion or glucose metabolism in posterior (i.e. occipital, parietal, and temporal) regions, and decreased activation of similar regions in functional MRI visual stimulation paradigms (Okada *et al.*, 1999; Stebbins *et al.*, 2004; Matsui *et al.*, 2006; Boecker *et al.*, 2007; Meppelink *et al.*, 2009). Together, these neuroimaging studies suggest that structural abnormalities in the brain's

visual processing areas may not only form the basis for these abnormally decreased metabolic or cortical activation patterns, but also might even explain the clinical presentation of visual rather than non-visual hallucinations. The exact mechanisms by which these structural, metabolic, or functional aberrations relate to the severity of visual hallucinations in Parkinson's disease are not fully elucidated. In our study, 4 of 18 identified regions of grey matter atrophy in the Parkinson's disease hallucinators (i.e. left inferior parietal lobule, left cuneus, right lingual gyrus, and right precentral gyrus) showed the greatest relationship to hallucination severity scores. The majority of these areas perform different roles in the visuoperceptive system, ranging from processing of visual stimuli (e.g. cuneus and lingual gyrus) to integrating multi-modal information. The inferior parietal lobule, in particular, may play a pivotal role in the presence and severity of visual hallucinations in Parkinson's disease due to its connectivity to multiple other brain regions involved in a wide array of motor, sensory, language, and visual functions (Caspers *et al.*, 2013). It is not known, however, whether grey matter atrophy in visuoperceptive regions could be the consequence (rather than the cause) of long standing visual hallucinations in patients with Parkinson's disease. Multi-modal neuroimaging studies performed at the same time-point in hallucinators may help answer questions regarding the temporal relationship of structural changes to metabolic and functional abnormalities (i.e. do the decreased perfusion or activation patterns result from structural atrophy or might they occur at an early disease stage, before structural changes?).

Several theoretical explanations for visual hallucinations have been proposed. These include impairment in the visual system from the retina to higher-order visual processing; cortical release phenomena because of sensory deafferentation such as in the Charles Bonnet syndrome; cortical irritation or excitability; abnormalities in various perceptual, attentional, arousal or cognitive processes; or dysregulation of external perception and internal image production across the visual system, brainstem, subcortical and cortical regions (Collerton *et al.*, 2005; Diederich *et al.*, 2005; Shine *et al.*, 2011; Taylor *et al.*, 2011). Deficits in the primary visual system as a result of dopamine cell loss in the retina or structural changes in retinal thickness in Parkinson's disease may contribute to hallucinations (Altintas *et al.*, 2008; Archibald *et al.*, 2009; Moreno-Ramos *et al.*, 2013), and hallucinators exhibit reduced contrast sensitivity, colour discrimination, and visual acuity compared with non-hallucinators (Diederich *et al.*, 1998). Hallucinations may result from either increased misperceptions of visual stimuli in a visually-deprived environment or by the chronic deafferentation of higher-order visual regions. This chronic denervation could be hypothesized to lead to subsequent brain atrophy selectively in visuoperceptive regions. Other theories of hallucinations emphasize impairment in cognitive, attentional and visuoperceptive processes, spanning the neuroanatomical levels of the brainstem, subcortical and cortical regions. Each theory focuses on the relationship of hallucinations to distinct elements such as impaired arousal or vigilance, sleep-wake disturbances or dream intrusions, altered attention and/or specific cognitive processes (e.g. set-shifting, executive functions, or visuospatial abilities), abnormal inference and modulation of internal and external perceptions, or altered higher-order visuoperceptive processing (Collerton

et al., 2005; Diederich *et al.*, 2005; Shine *et al.*, 2011; Onofrij *et al.*, 2012). Our structural MRI findings with abnormalities in primarily 'what' and 'where' visuoperceptive regions, best fit with the bottom-up model of altered visuoperceptive processing, but also share features of impaired attentional models of Parkinson's disease hallucinations. Regional atrophy also occurred in the inferior parietal lobule and cingulate gyrus, which are two areas implicated in visuoperceptive processing, visuospatial orientation, and visual memory, but also multi-sensory integration, attentional, and emotional processes. Structural abnormalities in the visuoperceptive pathways and 'hub' regions suggest that there may be a 'disconnection' between posterior and anterior parts of the brain in hallucinators, as seen in several metabolic and functional neuroimaging studies. Future integrated studies using multi-modal structural, functional, and metabolic neuroimaging techniques; physiological measures of vision and sleep/arousal; and experimental attentional, cognitive, and visuoperceptive tasks may provide insights into how these various theories contribute to the development of hallucinations in Parkinson's disease.

To date, there have been few neuropathological studies of subjects with Parkinson's disease with hallucinations. In those clinico-pathological studies that were carried out, Lewy bodies were reported in the amygdala, parahippocampus, frontal and parietal lobes, and inferior temporal cortex in Parkinson's disease hallucinators (Harding *et al.*, 2002; Papapetropoulos *et al.*, 2006). Interestingly, the inferior temporal cortex comprises part of the ventral stream visuoperceptive pathway responsible for representation of complex object features and facial perception. However, Lewy bodies were negligible in the occipital lobe in one study (Harding *et al.*, 2002) and not examined in the other (Papapetropoulos *et al.*, 2006). Small sample sizes, presence of cognitive deficits or dementia in the hallucinators, and overall more advanced disease at death, however, pose challenges for parsing out neuropathological changes specific to hallucinations. These findings also suggest that other neuropathologies, neurochemical alterations [i.e. abnormal serotonergic (Huot *et al.*, 2010, 2012) or cholinergic receptor binding (O'Brien *et al.*, 2008)], or disrupted white matter pathways (i.e. inferior longitudinal fasciculus; Kantarci *et al.*, 2010) may play a role in the atrophy in occipital and related visuoperceptive regions found on structural MRI of Parkinson's disease hallucinators.

In our study, in addition to grey matter volume loss predominantly in visuoperceptive areas in the hallucinators compared to the non-hallucinators, we detected reduced grey matter volume in the precentral gyrus (premotor cortex). Although the two Parkinson's disease groups did not differ significantly in motor scores (as measured by the MDS-UPDRS part III and by Hoehn and Yahr stage) or in disease duration, the hallucinators had slightly longer disease durations (mean 13.1 ± 4.6 years versus 10.8 ± 4.4 years). Considering clinico-anatomical correlates, we hypothesize that the greater precentral gyrus atrophy in the hallucinator group might possibly relate to their slightly longer disease course or to a greater degree of motor dysfunction that was not captured by the demographic or disease-related variables of interest in our study.

We acknowledge that there are some study limitations including a relatively small sample size, which although smaller than in one

study (Shin *et al.*, 2012), is larger than in several previously published structural MRI studies (Ramirez-Ruiz *et al.*, 2007; Ibarretxe-Bilbao *et al.*, 2008, 2010; Janzen *et al.*, 2012). Even so, larger sample sizes of cognitively well-matched hallucinators and non-hallucinators are needed to validate these grey matter atrophy results with more stringent statistical corrections, which minimize potential false-positives. Our findings of distinct structural MRI brain-behaviour correlates for hallucinations and dementia, however, may generate hypotheses and new models regarding these two frequent and disabling complications in Parkinson's disease. At present, we cannot establish the underlying neuropathology associated with the grey matter atrophy detected on MRI, but future post-mortem studies will be informative. Although the Parkinson's disease groups were matched on cognitive deficits and age, they were not matched for use of antipsychotic medications. It is notable that even when some of the hallucinators were treated for the condition, the underlying structural abnormalities were evident. Whether antipsychotic treatment *per se* can produce structural changes on brain MRI remains a question for future studies of Parkinson's disease hallucinators. Lastly, we cannot confirm that the Parkinson's disease non-hallucinators will never become hallucinators. Planned longitudinal follow up studies with careful monitoring will permit assessment of 'conversion' and clinical and neuroimaging risk factors.

In conclusion, the structural abnormalities detected in subjects with Parkinson's disease with current and chronic visual hallucinations suggest that there are distinct regional patterns of grey matter atrophy associated with visual hallucinations in Parkinson's disease, independent of cognitive impairment or dementia. Reduced grey matter in these brain regions that subserve visuoperceptive functions may contribute to aberrant processing of visual input, especially in the ventral 'what' and dorsal 'where' visual streams and thus, lead to the clinical manifestations of visual hallucinatory phenomena in Parkinson's disease. These neuroanatomical findings provide the basis for future studies investigating the role of neural network dysfunction in visual hallucinations in Parkinson's disease and ultimately, providing patients with novel therapies that target hallucinations and visuoperceptive dysfunction.

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