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Resting activity in visual and corticostriatal pathways in Parkinson's disease with hallucinations

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ABSTRACT

Background: Visual hallucinations are an important non-motor complication of Parkinson's disease (PD) and carry a negative prognosis. Their biological basis is uncertain, but may relate to the activity of resting state networks in brain. We therefore aimed to investigate functional activity of brain in patients with visual hallucinations (PDVH) in resting state compared to patients without hallucinations (PDnonVH) and a healthy control group (HC).

Methods: Resting state functional MRI was acquired and the primary analysis compared the amplitude of low-frequency fluctuations (ALFF) across groups. This informed a secondary analysis, in the PD groups only, comparing functional connectivity between a 'seed' region in the occipital lobe and the rest of the brain.

Results: Individuals with PDVH showed lower ALFF in bilateral lingual gyrus and cuneus and greater ALFF in temporo-parietal regions, medial temporal gyrus and cerebellum than PDnonVH and HC. PDnonVH also had lower ALFF in occipitoparietal region and greater ALFF in medial temporal gyrus, temporo-parietal and cerebellum regions than HC. Functional connectivity analysis revealed that, although both PD groups had lower occipital functional connectivity relative to the HC group, occipital – corticostriatal connectivity was significantly higher in those with PDVH compared with PDnonVH.

Conclusion: Our study reveals widespread hemodynamic alterations in PD. However, within a functionally abnormal occipital lobe, those with PDVH have even lower ALFF than non-hallucinators, but have higher occipital functional connectivity with cortical-striatal regions. These findings suggest disruption of pathways underpinning both primary visual perceptual and intrinsic visual integration may contribute to visual hallucinations in PD.

1. Introduction

Parkinson's Disease (PD) is classically regarded as a motor disorder, but non-motor manifestations also occur [1]. One of the most common and striking features is visual hallucinations [2]. Visual hallucinations affect 20–75% of patients with PD, and predict dementia and mortality [3]. The underlying biology of visual hallucinations in PD remains poorly understood but is thought to involve functional abnormalities in primary visual cortex along with altered activity in visual associative cortices [4]. Altered task-

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dependent hemodynamic activity has also been observed in frontal and subcortical regions in individuals with PD and visual hallucinations (PDVH) [5,6], suggesting that top-down regulatory processes may contribute [7]. However, the direction of findings reported in functional studies has not always been consistent. This is likely to be at least partly due to the distinct demands of different task designs, therefore an investigation of baseline function is of potential clinical value.

We previously examined activity within the default mode network in PDVH. We found that PDVH had greater coactivation within this network compared to PD patients without visual hallucinations (PDnonVH) [8]. We also reported disrupted functional connectivity between frontal regions and the hippocampus in PDVH [9]. We interpreted these findings as supporting the hypothesis of interrupted top-down processing in PDVH [7]. However, we did not examine whole brain functional activity in PDVH.

Amplitude of low-frequency fluctuation (ALFF) has been developed by Zang et al. [10] to measure whole-brain resting-state (rs)-fMRI. ALFF has been linked to neuronal glucose metabolism [11] and correlates with local field potential activity [12]. Alterations in ALFF have described in a number of disorders including schizophrenia and major depressive disorder [13,14], making the patterns of ALFF alterations potentially useful biomarkers for complex neuropsychiatric conditions. In this study, we first compared resting whole brain activity in individuals with PD with and without visual hallucinations and an unaffected elderly control (HC) group. We then examined resting state functional connectivity between a 'seed' region, defined by result of the ALFF analysis, and the rest of the brain. We hypothesized that the PDVH would have altered ALFF in visual cortices reflecting a deficit in visual processing. In addition, we predicted that there would be functional connectivity abnormalities between primary visual cortex and 'higher-order' brain regions in PDVH.

2. Materials and methods

2.1. Participants

Eligible patients were referred by the Movement Disorders Clinic by the attending neurologist, whilst HC were recruited from the patient's social network or the local community by advertisement. Parkinson's disease was diagnosed according to the criteria of the UK Parkinson's Disease Society Brain Bank. The assessments included the following: Hoehn and Yahr Scale [15] to assess stage of illness; Unified Parkinson's Disease Rating Scale (UPDRS; Fahn et al., 1987), part III to evaluate motor symptom severity; Montgomery–Åsberg Depression Rating Scale – Self-assessment (MADRS-S) [16] to rate depressive symptoms; Mini-Mental State Examination (MMSE) [17] to assess cognitive impairment; and the Parkinson Psychosis Rating Scale (PPRS) [18] to assess psychosis. The PPRS includes a detailed description of visual hallucinations recorded from patients and caregivers. Patients were recruited who experienced repetitive and complex visual hallucinations usually reporting seeing these as well-formed persons, animals or objects, lasting for at least 4 weeks and occurring at least once every 4 weeks. Exclusion criteria were: neurological disorders other than Parkinson's disease; other psychiatric disorders; mild to moderate depressive symptoms (MADRS >6); severe cognitive impairment if the MMSE <24. All participants were right handed. A levodopa equivalent dose (levodopa and dopaminergic agonists) was calculated as described in the literature [19].

All participants were reimbursed for travel expenses and signed informed consent for participation. The study was ethically approved by the local Institutional Review Board. Demographic and clinical characteristics are described in Table 1.

2.2. MRI data acquisition

Resting functional MRI data were acquired by a 3T scanner (Achieva; Philips Healthcare, Hong Kong) using the 8-channel phased-array head coil with patients in the supine position. The functional imaging data were acquired using a gradient-echo echo-planar imaging (EPI) sequence sensitive to BOLD contrast. Acquisition parameters were: TR = 1800 ms; TE = 30 ms; flip angle = 90°; 220 volumes; 45 axial slices; anterior-posterior acquisition; in-plane resolution = 3.75 × 3.75 mm; slice thickness = 4 mm; field of view = 240 × 180 × 240 mm; acquisition time = 6.6 min. Slice acquisition order was contiguous. Earplugs were used to reduce scanner noise and head motion was restricted by a foam pillow as well as extendable padded head clamps. Participants were asked to simply rest in the scanner with their eyes closed before each resting state scan and not fall asleep while remaining as still as possible.

Table 1
Demographic and clinical profile of HC, PDnonVH and PDVH.

Demographics	HC (SD) ($n = 14$)	PDnonVH (SD) ($n = 12$)	PDVH (SD) ($n = 12$)	p-value
Age	64.1 (4.0)	63.4 (7.4)	67.6 (7.4)	0.234
Gender (females/males)	8/6	8/4	9/3	0.631
Duration of illness (years)	n/a	8.4 (5.1)	10.0 (3.5)	0.400
Duration of VH (months)	n/a	n/a	22.6 ± 17.3	n/a
Hoehn and Yahr stage	n/a	2.8 (0.9)	3.2 (0.7)	0.160
UPDRS-III score	n/a	18.0 (12.9)	20.9 (10.6)	0.553
Levodopa dose (mg)	n/a	704.9 (519.4)	978.7 (361.3)	0.148
Affected body side (R/B/L)	n/a	6/1/5	4/3/5	0.497
MMSE score	29.1 (0.7)	28.5 (1.7)	27.6 (2.4)	0.092
MADRS-S score	0.4 (0.7)	1.2 (1.8)	2.2 (2.0)	0.025[a]
PPRS score (6–24)	6.1 (0.3)	6.4 (0.6)	8.7 (1.2)	<0.001[b]

Continues data are presented in mean ± SD.
MMSE, Mini-Mental State Examination; MADRS-S, Montgomery–Åsberg Depression Rating Scale – Self-assessment; UPDRS, Unified Parkinson's Disease Rating Scale; PPRS, Parkinson Psychosis Rating Scale; PANSS, The positive and negative syndrome scale; HC, healthy control; PDnonVH, Parkinson's disease without visual hallucination; PDVH, Parkinson's Disease with visual hallucination. R, right side; L, left side; B, both. n/a = not applicable; p values of two group comparisons were calculated using Independent-Samples t-tests (chi-squared test for gender and affected body side); p values of three group comparisons were calculated using one-way ANOVA.
[a] $p < 0.05$.
[b] $p < 0.01$.

Three-dimensional T1-weighted anatomical MRI were also acquired with fast field echo sequence (Magnetization Prepared Rapid Gradient Echo, MPRAGE), with the parameters: TR = 6895 ms; TE = 3.16 ms; FA = 8°; 1 × 1 × 1 mm voxels; FOV = 250 × 250 × 155 mm; number of slices = 155.

2.3. Functional imaging analysis

2.3.1. Image preprocessing of resting fMRI

Preprocessing was performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). First, all functional images were corrected for slice timing and head movement. Functional scans with excessive head movement >2.5 mm of displacement or >2.5° of rotation in any direction were discarded. Prior to band-pass filtering (0.01–0.08 Hz), the following nuisance covariates were regressed from the BOLD signal: six rigid–body parameters; white matter signal; cerebrospinal fluid signal. After generation of ALFF and functional connectivity, all functional data were normalized to the Montreal Neurological Institute (MNI) space by applying the transformation parameters obtained from the structural images (see the following "structural image analysis" section for details) to those time and motion corrected and nuisance covaried images, resampled (3 × 3 × 3 voxels) and smoothed (4-mm full width at half maximum (FWHM) Gaussian kernel).

2.4. ALFF calculations

At each voxel the BOLD time series was first converted to the frequency domain using a Fast Fourier Transform and the square root of the power spectrum was computed and then averaged across a specified frequency range (0.01–0.08 Hz) to remove residual low and high frequency noise in resting state. Once transformed by Fisher's Z to reduce the global effects of variability across participants, this value is referred to as the ALFF for a given voxel [10]. Calculations were made using REST software version 1.8 (www.restfmri.net) [20].

2.5. Functional connectivity of the occipital seed

Functional connectivity was based on a seed-region approach and conducted in MNI space. The area in occipital lobe with a significantly lower ALFF signal in the PDVH compared to PDnonVH was selected as the seed region. For all participants, mean occipital time series extracted from the seed region were correlated with the time series at all other brain voxels using Pearson's coefficient of correlation followed by Fisher's r-to-z transformation.

2.6. Structural image analysis

Individual structural T1-weighted images were co-registered to the mean motion-corrected functional images using a linear transformation. They were then segmented into gray matter, white matter (WM), and cerebrospinal fluid (CSF) in MNI space by using "New Segment" in SPM8. DARTEL [21] was then used to create a study-specific template. GM, WM and CSF were then normalized to MNI space and smoothed with an 8-mm FWHM Gaussian kernel. Mean modulated and smoothed GM maps (intensity threshold = 0.2) were used to generate a group GM mask and