The relationship between hallucinations and FDG-PET in dementia with Lewy bodies

Michael J. Firbank,[1] Jim Lloyd,[2] John T. O'Brien[3]

1 Institute for Neuroscience and Newcastle University Institute for Ageing, Campus for Ageing and Vitality, Newcastle University, Newcastle upon Tyne, UK
2 Nuclear Medicine Department, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
3 Department of Psychiatry, University of Cambridge School of Clinical Medicine, Box 189, Level E4, Cambridge Biomedical Campus, Cambridge, UK

Corresponding author

Michael Firbank

Michael.firbank@ncl.ac.uk

Institute of Neuroscience
Newcastle University
Campus for Ageing and Vitality
Newcastle upon Tyne,
NE4 5PL Tel: +44 (0)191 208 1319

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ABSTRACT

Objective: Visual hallucinations are common in dementia with Lewy bodies (DLB), although their etiology is unclear. This study aimed to investigate the relationship between severity and frequency of hallucinations and regional brain glucose metabolism.

Methods: We performed brain FDG-PET scanning on 28 subjects with DLB (mean age 76). The neuropsychiatric index (NPI) was used to assess frequency and severity of hallucinations. We used the SPM package to investigate voxelwise correlations between NPI hallucination score (severity x frequency) and FDG uptake relative to the cerebellum.

Results: There was a bilateral medial occipital region where reduced FDG was associated with increased hallucination severity and frequency.

Conclusion: The reduced occipital metabolism frequently seen in DLB is associated with frequency and severity of visual hallucinations. Further studies are required to investigate whether this is the result of deficits in top-down or bottom-up visual processing pathways.

INTRODUCTION

Visual hallucinations are a common and distressing feature in DLB, but their etiology is still unclear (Onofrj et al. 2013). Although reduced occipital and parietal perfusion, and glucose metabolism, are well documented in DLB compared to healthy subjects, (Colloby et al. 2002; Ishii et al. 1999; O'Brien et al. 2014) few studies have investigated the relationship with hallucinations within DLB subjects, and results have been mixed. We investigated the relationship between hallucinations as measured by the neuropsychiatric inventory, and FDG-PET brain imaging in a cohort of patients with DLB. We hypothesised that more severe hallucinations would be associated with reduced glucose metabolism in visual processing areas.

METHODS

Subjects

Subjects were part of a study investigating the relative performance of FDG-PET vs perfusion SPECT in the diagnosis of AD and DLB. Main results from the study have been reported elsewhere (O'Brien et al. 2014). The study subjects were recruited prospectively from people aged over 60 with mild to moderate dementia (MMSE>12) referred to clinical services in North-East England. In this report, we only examined the subjects who met criteria for probable DLB (McKeith et al. 2005). The study was approved by the local Ethics Committee, and all participants (or nominated Independent Mental Capacity Advocate where participant lacked capacity) gave informed consent before participating.

Clinical diagnosis was made by consensus between 3 experienced clinicians. All subjects had to have sufficient command of English and adequate visual and auditory acuity to allow cognitive and neuropsychological testing. Exclusion criteria were a) past history of alcohol or drug dependence; b) contraindications for FDG-PET scanning (e.g. inability to lie flat); c) fasting blood glucose level > 180 mg / dL. We recruited 30 subjects with DLB who were successfully scanned with FDG-PET-CT.

Subjects underwent detailed neuropsychiatric investigation including the Cambridge Cognitive Examination (CAMCOG). Parkinsonian motor features were assessed in all subjects using the motor subsection of the Unified Parkinson's Disease Rating Scale (UPDRS III). To assess hallucinations and other neuropsychiatric features occuring in the month before assessment, we performed the Neuropsychiatric inventory (NPI) (Cummings et al. 1994). The NPI was not done in one subject due to lack of a suitable informant, and this subject was excluded from the analysis. An additional subject was excluded as the reported hallucinations were of a non visual nature, leaving 28 in the analysis.

Scanning

FDG-PET head scans were done over 10 min using a Siemens Biograph Truepoint FDG-PET-CT starting 30 min after iv administration of 250 MBq F-18 FDG. Siemens software was used for

iterative reconstruction with scatter and attenuation correction based on the CT scan data obtained immediately before the FDG-PET scan. Patients were injected in quiet surroundings with minimal distractions and eyes open.

SPM analysis

As described in more detail elsewhere, (O'Brien et al. 2014) the PET scans were non-linearly spatially normalised to a study specific template. Scans were intensity normalised to the mean within a cerebellar region-of-interest (ROI) and smoothed with a 8mm Gaussian. SPM8 (www.fil.ion.ucl.ac.uk/spm) was used to perform a voxelwise correlation between NPI hallucination score and normalised FDG intensity with additional covariates of CAMCOG, UPDRS III and disease duration. The statistic images were thresholded at $p < 0.001$ voxelwise, and clusters taken to be significant at $p < 0.05$ FWE (familywise error) corrected for multiple comparisons. The SPM Anatomy toolbox was used to identify anatomic labels for significant clusters.

RESULTS

Table 1 shows the subject demographics. There were 8 subjects in whom hallucinations were not reported on the NPI, 11 with purely visual hallucinations, and 9 with visual plus auditory or tactile hallucinations. Supplementary table 1 shows the distribution of NPI frequency and severity scores. Figure 1 and supplementary table 2 show the results of the SPM analysis. There was a significant bilateral cluster which showed decreased FDG uptake with increasing NPI hallucination frequency x severity score in the occipital lobe, which was 51% in Area 17, 23% in Area 18, and 15% V3v. Analysis of the severity and frequency hallucination NPI scores separately produced very similar results, with both scores correlating with occipital hypometabolism (supplementary figure 1). There were no significant clusters elsewhere, nor any regions where increased FDG uptake correlated with increased NPI hallucination score.

Table 1: Demographics on the 28 subjects included.

	Mean (SD)
Age	76.4 (6.0)
Sex (F/M)	5/23
Duration illness (months)	39.3 (27.9)
CAMCOG	72.1 (13.4)
MMSE score	21.7 (4.2)
NPI_Halltot	2.43 (2.69)
NPI Hallucination frequency	1.86 (1.58)
NPI Hallucination severity	0.93 (0.81)
UPDRS III	25.8 (11.8)

DISCUSSION

We found a significant relationship between hallucination severity and reduced glucose metabolism in the primary visual cortex of subjects with DLB.

We are only aware of two studies which have directly investigated the relationship between occipital hypometabolism and hallucinations. Perneczky et al. (2008) found reduction in the occipito-temporal region in those DLB with hallucinations vs. without, whilst Imamura et al. (1999) found reduced occipital metabolism in all DLB subjects, but those with hallucinations had relatively preserved posterior temporal and parietal metabolism compared to non-hallucinators. A small study of FDG in DLB (Okamura et al. 2001) found reduced uptake in the visual association cortex of the DLB group compared to the AD group irrespective of clinical severity of the disease.

Using perfusion SPECT, a number of studies (Colloby et al. 2002; Ishii et al. 1999) report reduced occipital perfusion in DLB, but do not mention whether this correlated with hallucination severity. Pasquier et al. (2002) found lower perfusion of the occipital region in DLB with vs. without hallucinations, however, Lobotesis et al. (2001) found reduced occipital perfusion in DLB overall, but no difference between those with or without hallucinations.

Possible explanations for the reduced occipital glucose metabolism include pathological changes to the occipital lobe itself, or disrupted top-down feedback from higher visual areas. Alterations to the cholinergic neurotransmitter system have been observed in the occipital lobe of DLB (Mukaetova-Ladinska et al. 2013).

Two studies have examined DLB patients with visual hallucinations before and after treatment with donepezil. These studies found that donepezil decreased the severity of hallucinations, but found conflicting imaging results, with one reporting occipital perfusion increased after treatment, (Mori et al. 2006) but the other decreased glucose metabolism (Satoh et al. 2010).

A limitation of our study is that we did not record the presence of hallucinations during the scan, and the NPI refers to hallucinations during the preceding month. Hence our finding can only be related to a tendency for patients to hallucinate, rather than directly associated with hallucinations.

One difference between our study and most previous ones, is that our scans were done with eyes open compared to eyes closed. The eyes open state is associated with increased occipital FDG uptake as well as increased functional connectivity between the occipital cortex and other brain regions (Riedl et al. 2014). Our results are therefore consistent with disrupted connectivity between the primary visual cortex and higher visual regions being associated with hallucinations. This is further supported by our previous finding that in an fMRI study of visual function the primary visual cortex activation was normal in DLB, whilst higher visual areas were abnormal, (Taylor et al. 2012) and a recent MRI study found correlation between NPI hallucination score and reduced cortical thickness in the superior parietal region of DLB.

It is possible that differences in occipital FDG uptake between eyes open and eyes closed may reflect upon dysfunction in the bottom-up visual system, with those without hallucinations perhaps showing relatively increased uptake on eyes opening due to the increased input from the eye. This may account for differences between our study (eyes open, and hallucinators showing reduced occipital FDG) and that of Imamura et al. (1999) (eyes closed, no occipital difference with hallucination). However, further studies are needed to clarify the relationship between low medial occipital metabolism and hallucinations.

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FIGURES

Figure 1 Significant (voxelwise p <0.001 [t>3.4]) clusters for correlation of NPI-hallucination score (severity x frequency) and FDG uptake (normalised to cerebellum) , with additional covariates of UPDRS, disease duration and CAMCOG. Results overlaid on mean FDG-PET scan of participants. Scale shows T statistic. Crosshair on the significant left occipital cluster.

Compliance with Ethical Standards

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Conflict of Interest: JOB report grants and other from GE Healthcare, grants and other from Lilly, other from Bayer Healthcare, other from TauRx, other from Cytox, outside submitted work. MF and JL declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by Newcastle and North Tyneside Research Ethics Committee (REF 09/H0906/88), and all participants (or nominated Independent Mental Capacity Advocate where participant lacked capacity) gave informed consent before participating.

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