Occipital lobe and posterior cingulate perfusion in prediction of dementia with Lewy body pathology in a clinical sample

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# Abstract

**Objectives:** To investigate the diagnostic value of occipital lobe and posterior cingulate perfusion in predicting dopamine transporter imaging outcome using a quantitative measure of analysis.

**Methods:** Ninety-nine patients with cognitive complaints who had undergone both HMPAO-SPECT and 123I-FP-CIT imaging in a dementia diagnostic centre were analysed. Measures of perfusion were calculated from HMPAO-SPECT images for medial and lateral occipital lobe, posterior cingulate cortex, precuneus and cuneus regions of interest using SPM8. DaTscan images were quantified and specific binding ratios were calculated independent from HMPAO-SPECT results. Statistical parametric mapping and tests of associations between perfusion and 123I-FP-CIT imaging were completed.

**Results:** Regions of interest on HMPAO gave poor predictive values when used independently to predict 123I-FP-CIT status, however, the combination of normal posterior cingulate perfusion combined with medial and lateral occipital hypoperfusion was significantly associated with 123I-FP-CIT status, χ2(1, *N=*99) =9.72, *P =* .002. This combination also gave a high positive likelihood ratio and specificity (11.1, 98%). Sensitivity was however low (22%). No significant perfusion differences were found when abnormal and normal 123I-FP-CIT groups were directly compared using voxel based morphometry (p<0.05 FWE).

**Conclusion:** The combination of medial and lateral occipital hypoperfusion with preserved posterior cingulate gyrus perfusion is highly specific for individuals with a positive 123I-FP-CIT scan in a clinical sample where diagnostic doubt exists. This regional combination however lacks sensitivity; therefore, absence of the sign cannot be used to rule out dementia with Lewy bodies (DLB). A positive finding provides strong evidence to rule in DLB.

**Keywords:** Single-Photon Emission-Computed Tomography; Radiopharmaceuticals; Diagnostic Imaging; Lewy Body Dementia; Diagnosis, Differential;

# Introduction

Dementia with Lewy bodies (DLB) is the second most prevalent neurodegenerative dementia behind Alzheimer’s disease (AD), with an estimated 10-20% of people with dementia having DLB. Core criteria for DLB diagnosis include progressive cognitive decline with executive function, visuospatial and attentional deficits, in addition to hallucinations and parkinsonian symptoms (1,2). As DLB often presents with clinical and pathological features comparable to AD, Parkinson’s disease (PD) and vascular dementia (VaD), diagnosis may be difficult, and clinical misdiagnosis can occur (3). Early and accurate diagnosis is important for providing optimum clinical management to patients, including initiation of medications and appropriate care provisions. This can be particularly important for DLB management, where patients may be hypersensitive to anti-psychotic medication (4).

123I-FP-CIT single photon emission computed tomography (DaTSCAN) imaging is an established biomarker for antemortem diagnosis in DLB, and is included in the current consensus diagnostic criteria (2). It has good sensitivity and specificity for distinguishing DLB from AD, and other forms of dementia compared with both clinical and neuropathologically validated diagnosis (5–7). In clinical practice, when diagnosing dementia, it is often requested in conjunction with functional imaging techniques such as perfusion single photon emission computed tomography (SPECT) imaging, which are more useful at distinguishing non-DLB dementia subtypes.

Early DLB and AD patients often show a similar pattern of global cerebral perfusion, making differentiation between the subtypes difficult when the clinical presentation is similar (8). The presence of mixed pathology may also confound diagnosis in some cases (9). Previous studies have shown that regional analysis of occipital hypoperfusion, particularly of the medial region, on (99mTc) Hexamethylproyleneamine oxime (HMPAO) SPECT may be a specific biomarker for DLB, however its reliability in clinical settings is debated (8,10–12). DLB patients may also have relatively preserved function of the posterior cingulate in comparison to AD (the “posterior cingulate island sign”), where significant functional deficits are seen (13,14). The clinical utility of perfusion SPECT in identifying posterior cingulate preservation for DLB diagnosis is however also a point of contention (15). The combination of occipital regional functional deficits with preservation of posterior cingulate function could be a useful biomarker to distinguish DLB from AD, and reduce the need for further DaTSCAN imaging where functional imaging has already been completed (16).

Although previous studies have investigated the accuracy of perfusion SPECT and DaTSCAN imaging to distinguish DLB from AD, to our knowledge none have explored the use of quantitative region of interest analysis on perfusion SPECT imaging to predict DaTSCAN results in a mixed clinical sample. We aimed to investigate the extent to which *a priori* occipital and posterior cingulate regions of interests on HMPAO SPECT may be diagnostically specific for DLB in patients with abnormal DaTSCAN imaging. We hypothesised that the combination of these regions on HMPAO SPECT could accurately predict an individual’s DaTSCAN status, and therefore aid DLB diagnosis.

# Methods

## Sample

Ninety-nine patients with cognitive complaints who received both (99mTc) HMPAO SPECT and DaTSCAN imaging in a dementia diagnostic centre (University Hospital Southampton) as part of their clinical care were retrospectively identified. Images were obtained as per the NHS Health Research Authority approved Retrospective Brain Imaging in Dementia study (RetroBraIID). Patients were not selected by diagnosis to ensure results were applicable to a memory clinic setting, and diagnostic doubt existed for all patients at the time of scanning. The average time between HMPAO-SPECT and DaTSCAN acquisition was 105 days. Thirty-one HMPAO-SPECT controls were obtained for analysis. Control individuals did not have DaTSCAN imaging completed. A routine protocol restricts patient use of medications that could potentially interfere with tracer binding prior to scanning.

## DaTSCAN specific binding ratio quantification

The DaTSCAN images were acquired on a GE(SMV) DST-XL dual-head or Mediso Nucline x-Ring/4HR gamma camera with low energy high resolution collimators, using a 123I-FP-CIT tracer.A circular orbit was used and 128 projections were acquired producing a 128 x 128 matrix with a pixel size of 2.03 mm. OSEM reconstruction with 12 iterations and 8 subsets was completed, with a butterworth filter for 3D postfiltering.

DaTSCAN tracer uptake and binding was calculated for patients independently from (99mTc) HMPAO SPECT results using the specific binding ratio (SBR). Calculation of the SBR allows quantitative assessment of the dopaminergic function of the striatum in patients when compared to controls. The SBR is calculated using the specific uptake of the radioactive tracer (to the striata) and the non-specific uptake of the tracer (tracer not bound to striatal dopamine transporter and free tracer). A geometrical volume of interest covering the striatum captures all counts related to striatal binding, and non-specific counts are measured from a large volume of interest covering the whole cortex except for the striatum and edge of the cortex. The SBR is then calculated as the ratio of concentration of specific to non-specific radioactivity, as described by Bolt et al (17).

## Perfusion SPECT imaging

Perfusion SPECT imaging was completed in all cases using a 99mTc-hexamethylpropyleneamine oxime (HMPAO) tracer. Image acquisition, reconstruction and processing was identical for patients and controls. Images were taken on a GE(SMV) DST-XL dual-head gamma camera which had low-energy, high resolution collimators.An elliptical orbit was used and 128 projections were acquired producing a 128 x 128 matrix with a pixel size of 3.38 mm. The images were checked for movement and reconstructed using a filtered back projection method with attenuation correction.

In preparation for statistical analysis, the HMPAO-SPECT reconstructed images were spatially normalised and smoothed with a 14mm Gaussian kernel using statistical parametric mapping 8 (SPM8; 19). Count normalisation using the cerebellum as the reference region was completed using in-house MATLAB code. Correction for age was also performed.

*A priori* regions of interest (ROI) for the posterior cingulate, precuneus, medial occipital (calcarine fissure) and lateral occipital regions were created for each hemisphere using WFU-pickatlas software (19,20) and the automated anatomical labelling digital (AAL) atlas (22; Figure 1). Average voxel value counts were then obtained for each region of interest using the SPM8 marsbar toolbox for both patients and controls (22).

## Statistical analysis

Statistical analysis was completed using the Statistical Package for Social Sciences software (SPSS v22). Individuals were grouped into abnormal and normal DaTSCAN groups based on an age-dependent recommended cut-off 2 standard deviations away from the [123I]FP-CIT ENC-DAT normal database mean (23,24). DaTSCAN controls from the ENC-DAT normal database from which the cut-offs were derived were reconstructed and acquired in a manner compatible to the patient population (25).

Voxel based t-maps of the HMPAO scans comparing normal and abnormal DaTSCAN groups to each other and controls were produced using SPM8. SPM8 maps were extracted at a *P* < 0.05 family wise error (FWE) corrected significance with 100 cluster voxel threshold. (99mTc) HMPAO SPECT perfusion values for (1) individual ROIs, (2) combined occipital and posterior cingulate, and (3) combined posterior cingulate and precuneus ROIs, were compared between the DaTSCAN abnormal and normal groups using t-tests.

Finally, patients were grouped based on posterior cingulate, medial and/or lateral occipital, precuneus and cuneus perfusion both individually and in combination. We designated posterior cingulate preservation in combination with medial, lateral or whole occipital lobe hypoperfusion as PCing-MedOcc+, PCing-LatOcc+, and PCing-AllOcc+ respectively. We designated posterior cingulate preservation with precuneus hypoperfusion as PCing-Prec+, and posterior cingulate with precuneus and cuneus hypoperfusion as PCing-PrecCuneus+. Preserved posterior cingulate function was defined as an average perfusion voxel value less than two standard deviations away from control mean.

Cross-tabulation was used to evaluate the predictive power of posterior cingulate preservation, occipital lobe hypoperfusion and precuneus hypoperfusion both individually and combined in identifying DLB disease as defined by a positive (abnormal) DaTSCAN.

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| --- | --- | --- | --- | --- | --- |
| Table Demographic features of the sample  Abnormal DaTSCAN was defined as a specific binding ratio of more than 2 standard deviations (S.D) away from the [123I]FP-CIT ENC-DAT normal database mean (23). HMPAO-SPECT PCing-AllOcc+ was defined as an abnormal medial and lateral occipital perfusion (> 2 S.D below control mean) combined with a normal posterior cingulate cortex perfusion (< 2 S.D below control mean). Abbreviations: DaTSCAN, 123I-FP-CIT single photon emission computed tomography; SPECT, Single photon emission computed tomography; PCing, Posterior cingulate. | | | | | |
|  | DaTSCAN normal | DaTSCAN abnormal | HMPAO  non-  PCing-AllOcc+ | HMPAO  PCing-AllOcc+ | Statistics |
| Patients (Male) | 50 (30) | 49 (28) | 87 (50) | 12 (8) | - |
| Age in years (mean ± S.D) | 72.7 ± 10.1 | 71.9 ± 7.5 | 72.4 ± 8.6 | 71.9 ± 11.1 | *ns* |
| Months between HMPAO SPECT and DaTSCAN (mean ± S.D) | 3.1 ± 4.8 | 3.2 ± 4.8 | 3.2 ± 4.6 | 2.9 ± 4.0 | *ns* |

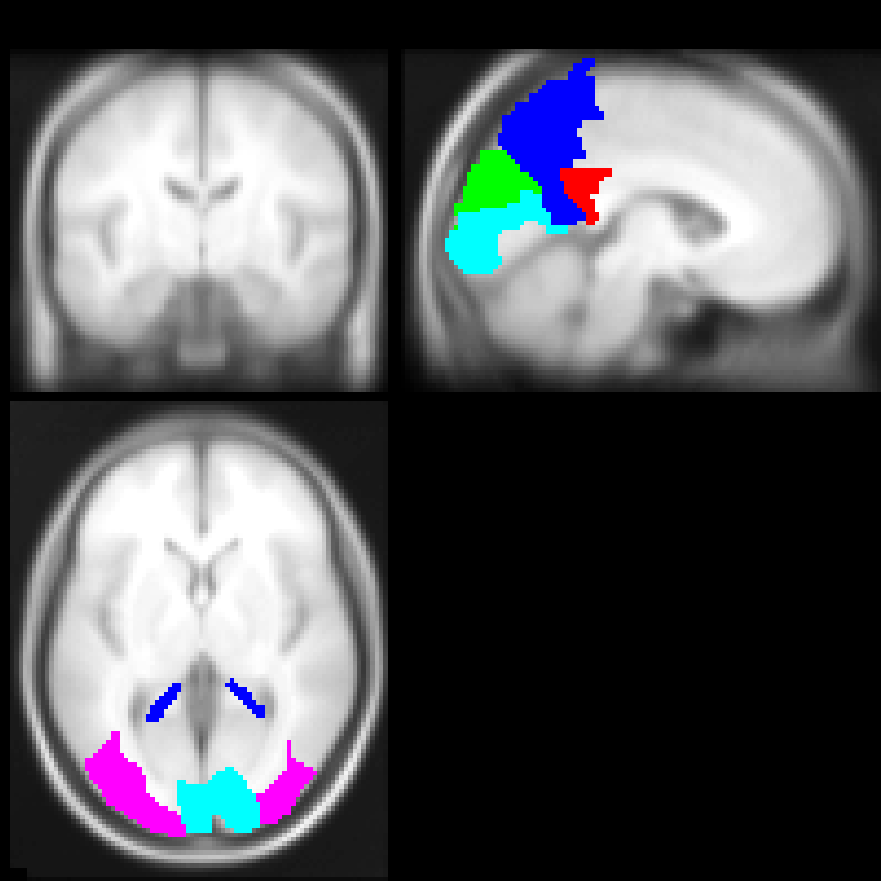
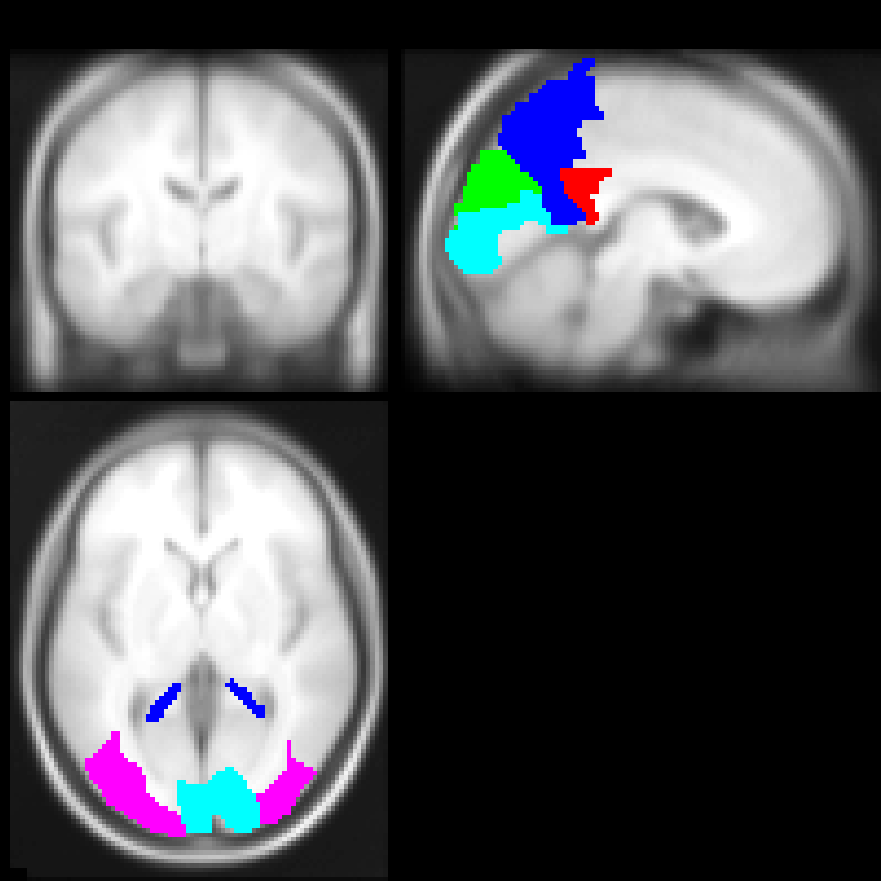


Figure Regions of interest used in the analysis

The regions of interest (ROIs) used in the analysis on axial and coronal slice view. The lateral occipital (violet), medial occipital / calcarine fissure (turquoise), posterior cingulate (red), cuneus (green) and precuneus (blue) is shown. The ROIs were obtained from the automatic anatomical labelling (aal) atlas, based in Montreal Neurological Institute (MNI) space.

# Results

## Group differences

Demographics of the sample can be seen in Table 1. When compared to controls using statistical parametric mapping, both normal (DaTSCAN negative) and abnormal (DaTSCAN positive) groups showed significant perfusion deficits with very similar regional abnormalities (*P* < .05 FWE corrected). The main areas of hypoperfusion included parietal, parietotemporal and occipital lobes, with further hypoperfusion in the superior frontal lobe, and superior posterior temporal lobe compared to controls. When perfusion deficits against controls for both groups were overlaid, deficits were more extensive in the abnormal DaTSCAN group, with extended hypoperfusion in the superior frontal lobe, medial prefrontal cortex and a region adjacent to the posterior cingulate (Figure 2). However, direct comparison of DaTSCAN groups showed no significant clusters at *P* < .05 FWE corrected threshold. No significant perfusion differences were found between DaTSCAN groups in any of the *a priori* ROIs defined when mean perfusion voxel values were compared using t-tests (*P* > .05).

|  |  |
| --- | --- |
|  |  |
|  |  |
| Figure Statistical parametric mapping DaTSCAN group against control comparisons.  Areas of hypoperfusion on HMPAO SPECT in DaTSCAN positive (red) and DaTSCAN negative (green) individuals when compared to controls. Areas of yellow indicate areas where hypoperfusion is present in both groups. *P* < .05 FWE corrected with 100 voxel cluster threshold. Abbreviations: DaTSCAN, 123I-FP-CIT SPECT; SPECT, Single photon emission computed tomography. | | | |

Table Accuracy of individual and combined regions in predicting 123I-FP-CIT SPECT (DaTSCAN) result

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Positive LR | Negative LR |
| Medial occipital | 39 | 60 | 49 | 50 | 0.969 | 1.02 |
| Lateral occipital | 61 | 36 | 48 | 49 | 0.957 | 1.08 |
| Posterior cingulate | 76 | 40 | 55 | 63 | 1.26 | 0.612 |
| Precuneus | 45 | 50 | 47 | 48 | 0.898 | 1.10 |
| PCing-MedOcc+ | 22 | 96 | 85 | 56 | 5.61 | 0.808 |
| PCing-LatOcc+ | 37 | 76 | 60 | 55 | 1.53 | 0.832 |
| PCing-AllOcc+ | 22 | 98 | 92 | 56 | 11.2 | 0.791 |
| PCing-Prec+ | 86 | 14 | 49 | 50 | 1.00 | 1.02 |
| PCing-PrecCuneus+ | 92 | 4 | 48 | 33 | 0.957 | 2.04 |

Sensitivity, specificity, postive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratios (LR) for individual and combined regions of interest in predicting DaTSCAN result. Medial and lateral occipital lobe hypoperfusion with preserved PCC perfusion (PCing-AllOcc+) was the most clinically useful predictor, with a large positive likelihood ratio. Preserved posterior cingulate (PCC) perfusion with medial occipital hypoperfusion (PCing-MedOcc +) gave better prediction than PCC preservation with lateral occipital hypoperfusion (PCing-LatOcc+). PCC to precuneus (PCing-Prec+) and precuneus and cuneus (PCing-PrecCuneus+) ratios were ineffective at predicting DaTSCAN group.

## Cross-tabulation

The combined *a priori* ROI DLB pattern of normal posterior cingulate perfusion with abnormal medial and lateral occipital perfusion (PCing-AllOcc+ group) showed very high specificity and positive prediction values for the presence of abnormal DaTSCAN (98% and 92% respectively), with a positive likelihood ratio of 11.1. Sensitivity and negative predictive values were however low (22% and 56% respectively). A Pearson Chi-square test of independence showed a significant relationship between DaTSCAN and HMPAO results, χ2(1, *N=*99) =9.72, *P =* .002.

When the medial and lateral occipital regions were examined individually with the posterior cingulate (PCing-MedOcc+ and PCing-LatOcc+ groups), the medial occipital region was more predictive than the lateral occipital region. PCing-MedOcc+ specificity and positive predictive value was only slightly reduced from the combined occipital regions (96% and 85%) and sensitivity and negative predictive values were similar (22% and 56%), with an overall positive likelihood ratio of 5.6 (Table 2).

Classifying patients using the precuneus to posterior cingulate perfusion ratio (PCing-Prec+ group) had high sensitivity, but very poor specificity of 14% and a positive and negative likelihood ratio of 1.0. Including the cuneus with the cingulate island sign and precuneus (PCing-PrecCuneus+) did not increase prediction accuracy. No individual regional biomarker could accurately predict DaTSCAN result.

# Discussion

This study aimed to elucidate the usefulness of occipital lobe and posterior cingulate gyrus perfusion on HMPAO SPECT in distinguishing DLB type dementia in diagnostically ambiguous clinical samples using nigrostriatal dopamine transporter imaging validation as gold standard. Our results show that the combination of reduced occipital lobe perfusion combined with preserved posterior cingulate perfusion (PCing-AllOcc+) in an individual is highly specific for DLB, despite visually near-identical group perfusion patterns in cognitively impaired individuals with abnormal, compared to normal, DaTSCANs. A high positive likelihood ratio highlights the potential clinical utility of this regional combination on HMPAO SPECT imaging to rule-in DLB.

The findings presented in this study highlight both the potential clinical use and the limitations of occipital lobe and posterior cingulate cortex ROI analysis on perfusion SPECT imaging for aiding DLB diagnosis. When compared to controls by statistical parametric mapping, both abnormal and normal DaTSCAN groups showed significantly reduced perfusion (*P* < .05 FWE corrected) across the cortex (Figure 2), with slight differences in superior frontal and medial regions only clearly visible upon direct overlay of the SPM maps. The similarity in hypoperfusion between the groups highlights the previously described difficulty for visual distinction between DLB and AD groups, particularly in clinical samples where mixed pathologies can exist (26).

Interestingly, direct voxel based comparisons of the DaTSCAN groups at standard corrected thresholds (*P* < .05 FWE) did not highlight hypoperfusion in the occipital lobe for the DLB group over non-DLB as previously shown in multiple studies (8,27–29), nor did they identify posterior cingulate preservation (30). Comparison of the mean perfusion voxel values also found no difference between groups in either individual or combined ratio ROIs. This may be due to these biomarkers being present in some, but not all, DLB patients, with group comparisons masking abnormality in some individuals. This is consistent with studies that have found both occipital lobe hypoperfusion and preservation of the posterior cingulate gyrus to be unreliable clinical biomarkers for DLB on perfusion SPECT imaging (12,15,31,32).

Despite the absence of significant DaTSCAN group differences in any of the a *priori* regions, the combination of lateral and medial occipital lobe hypoperfusion with normal posterior cingulate perfusion (PCing-AllOcc+) distinguished individuals with abnormal from normal DaTSCAN imaging with a high level of specificity in our unselected clinical sample. The high positive likelihood ratio of 11.1 suggests that the use of individual perfusion values to identify those with this pattern of perfusion could be a useful tool for aiding clinicians in the diagnosis of DLB when the clinical presentation is ambiguous for a dementia subtype. The medial occipital lobe was found to drive the predictor accuracy, a finding consistent with other studies that suggest that medial occipital lobe perfusion is preferentially reduced in DLB (33,34). The sensitivity and negative predictive value of the combined regions (PCing-AllOcc+) was however poor, and the classifier could not accurately predict a normal DaTSCAN result when the PCing-AllOcc+ regional combination was not present. We also found the combination of posterior cingulate to precuneus and cuneus ratio (PCing-Prec+ and PCing-PrecCuneus+) was ineffective in predicting DaTSCAN profiles in our sample, despite previous functional imaging studies suggesting their usefulness in the prediction of DLB over AD (13,16).

A recent study by Imabayashi et al (2016) using technetium-99m ethyl cysteinate dimer (ECD) SPECT and Z-score analysis in 17 AD and 18 probable DLB individuals found that medial occipital lobe hypoperfusion in combination with the cingulate island sign gave a high receiver operator characteristic curve area under the curve of 0.87 when classifying DLB individuals from amyloid positive AD patients (16). Although our findings do agree with the conclusion that the combination of these regions can be useful in clinical diagnosis of DLB, we found a much lower sensitivity in our sample (22% compared to 89%), suggesting the regions are not useful for predicting normal DaTSCAN (or non-DLB) individuals.

The difference in accuracy found is likely due to differing samples and classification of disease groups. Our large sample of individuals with diagnostic doubt were classified using DaTSCAN imaging, rather than classifying probable DLB individuals by clinical diagnosis alone. Additionally, we compared these DaTSCAN validated DLB individuals to any non-DLB diagnosis as diagnosed by a negative DaTSCAN, rather than amyloid validated AD only. A 2015 Cochrane review on the use of DaTSCAN imaging for classification of DLB concluded the technology was more accurate than consensus clinical criteria in discriminating DLB from AD (35).

Although we did not attempt to classify individuals with a negative DaTSCAN in our sample, the ability to predict an individual’s DaTSCAN status is directly useful for dementia clinicians in DLB diagnosis when diagnostic doubt exists. Our use of a naturalistic clinical sample should ensure results demonstrate the ROIs clinical utility.

The conflicting literature that exists on the usefulness of perfusion SPECT imaging in DLB diagnosis may be due to an inherent lack of resolution in the technology. Although semi-quantitative and quantitative analysis techniques such as SPM have been shown to improve diagnostic accuracy of HMPAO SPECT over visual assessment alone, FDG PET studies show consistently better sensitivity and specificity values for diagnosis of DLB with the use of occipital and/or posterior cingulate regions of interest (15,36). The use of a small and highly defined region of interest such as the posterior cingulate of the aal atlas may not be optimal for HMPAO SPECT, reducing accuracy for discrimination between DLB and other dementias.

There are several limitations to this study. The sample used was collected retrospectively from a clinical cohort, therefore long term follow up or histopathology to confirm diagnosis post imaging was not obtained. Although DaTSCAN imaging is widely regarded as the gold standard for antemortem DLB diagnosis, it is not 100% accurate, with an estimated 100% specificity and 88% sensitivity when assessed semi-quantitatively, as in this study, and validated with autopsy results (7). We note however, that clinical validation is less accurate than DaTSCAN imaging in diagnosis (35). Research into individuals with conflicting clinical profiles and DaTSCAN results are limited, however some individuals with atypical forms of DLB have been shown to have normal DaTSCAN imaging (37,38). We were unable to ascertain whether therapeutic medications were prescribed in the interval between the HMPAO SPECT and DaTSCAN. We do not believe this is likely to have a bearing on our results as medications usually prescribed in this situation, namely L-Dopa, dopamine agonists and cholinesterases are not believed to interfere with DaTSCAN binding (39–41). Finally, as with many imaging biomarkers, there is no consensus on the ideal cut-off value for either HMPAO SPECT perfusion values or the striatal binding ratio on DaTSCAN, and therefore 2 standard deviations away from controls may not be optimal for identification of DLB.

In conclusion, our findings show that the combination of medial and lateral occipital hypoperfusion with preserved posterior cingulate gyrus perfusion is highly specific for individuals with a positive DaTSCAN in a clinical sample where diagnostic doubt exists. This regional combination however lacks sensitivity and is present only in some DLB individuals, therefore absence of the sign cannot be used to rule out DLB. A positive finding provides strong evidence to rule in DLB.

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