INTERNAL MEDICINE JOURNAL

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doi:10.1111/imj.14890

ORIGINAL ARTICLE

Head-to-head comparison of cerebral blood flow single-photon emission computed tomography and ^{18}F-fluoro-2-deoxyglucose positron emission tomography in the diagnosis of Alzheimer disease

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Key words
Alzheimer disease, single-photon emission computed tomography imaging, positron emission tomography, ^{18}F-fluoro-2-deoxyglucose.

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Received 16 April 2020; accepted 7 May 2020.

Abstract

Background: Clinical diagnosis of Alzheimer disease (AD) is only 70% accurate. Reduced cerebral blood flow (CBF) and metabolism in parieto-temporal and posterior cingulate cortex may assist diagnosis. While widely accepted that ^{18}F-fluoro-2-deoxyglucose positron emission tomography (^{18}F-FDG PET) has superior accuracy to CBF-SPECT for AD, there are very limited head-to-head data from clinically relevant populations and these studies relied on clinical diagnosis as the reference standard.
Aims: To compare directly the accuracy of CBF-SPECT and ^{18}F-FDG PET in patients referred for diagnostic studies in detecting β-amyloid PET confirmed AD.
Methods: A total of 126 patients, 56% with mild cognitive impairment and 44% with dementia, completed both CBF-SPECT and ^{18}F-FDG PET as part of their diagnostic assessment, and subsequently underwent β-amyloid PET for research purposes. Transaxial slices and Neurostat 3D-SSP analyses of ^{18}F-FDG PET and CBF-SPECT scans were independently reviewed by five nuclear medicine clinicians blinded to all other data. Operators selected the most likely diagnosis and their diagnostic confidence. Accuracy analysis used final diagnosis incorporating β-amyloid PET as the reference standard.
Results: Clinicians reported high diagnostic confidence in 83% of ^{18}F-FDG PET compared to 67% for CBF-SPECT ($P = 0.001$). All reviewers showed individually higher accuracy using ^{18}F-FDG PET. Based on majority read, the combined area under the receiver operating characteristic curve in diagnosing AD was 0.71 for ^{18}F-FDG PET and 0.61 for CBF-SPECT ($P = 0.02$). The sensitivity of ^{18}F-FDG PET and CBF-SPECT was 76% versus 43% ($P < 0.001$), while specificity was 74% versus 83% ($P = 0.45$).
Conclusions: ^{18}F-FDG PET is superior to CBF-SPECT in detecting AD among patients referred for the assessment of cognitive impairment.

Introduction

Dementia due to Alzheimer disease (AD) is a major public health issue affecting 1% of the population at age 60 then doubling in prevalence with every additional 5 years of age so that over 30% of individuals aged 85 years and older are affected.[1] Early and accurate diagnosis may allow better use of medications such as anticholinesterase inhibitors,[2] better preparation for future needs reducing patient and family stress, less repeat investigation and more participation in clinical trials.

The diagnosis of AD has traditionally relied on clinical and neuropsychological assessments in accordance with the original NINCDS-ADRDA criteria set in 1984.[3] However, these criteria require dementia that may take up to 5 years to develop after initial assessment and then only achieve sensitivity and specificity of 70% compared to post-mortem neuropathological diagnosis of AD.[4,5] Revised NINCDS-ADRDA criteria and NIA-AA workgroups, therefore, now recommend the incorporation of biomarkers into diagnostic paradigms when higher

Funding: None.
Conflict of interest: None.

accuracy is required.[6,7] Biomarkers assess the pathophysiological processes underlying AD development (e.g. β-amyloid and tau accumulation, hippocampal atrophy, parieto-temporal hypometabolism) and thereby aid in the differentiation of AD from other disorders.

Cerebral blood flow (CBF)-single-photon emission computed tomography (SPECT) and ^{18}F-fluoro-2-deoxyglucose positron emission tomography (^{18}F-FDG PET) are the most widely available nuclear medicine biomarkers for AD in clinical use. They assess cerebral perfusion and metabolism, respectively, with distinct patterns of functional change seen in AD (Figs 1,2) and other dementia syndromes. ^{18}F-FDG PET has demonstrated greater accuracy than initial clinical evaluation for diagnosis of AD compared to pathologic diagnosis.[8] ^{18}F-FDG PET has superior imaging characteristics compared to CBF-SPECT (Fig. 2), and meta-analyses of non-comparative studies have reported higher accuracy for the diagnosis of AD.[9] Head-to-head evidence is, however, limited, with few studies directly comparing the accuracy of CBF-SPECT and ^{18}F-FDG PET within the same patients.[10–19] A notable exception is a head-to-head study by O'Brien *et al.*, who compared the accuracy of ^{18}F-FDG PET and CBF-SPECT among three groups of patients; those with AD (n = 38), Dementia with Lewy bodies (DLB, n = 30) and healthy controls (n = 30).[16] ^{18}F-FDG PET was found to have superior accuracy in differentiating dementia versus no-dementia (area under the curve: 0.93 vs 0.72) and AD from DLB (AUC: 0.80 vs 0.58). The study did not, however, compare accuracy within a clinically referred cohort of patients, limiting the direct applicability of the results to both clinical practice and health economic modelling. Only two head-to-head studies have examined clinically referred subjects.[10,11] The findings were inconsistent, the sample sizes were small and accuracy was compared to clinical diagnosis despite its inherent limitations.

As a consequence of the paucity of clinically relevant, head-to-head data, many countries continue preferentially to use and fund CBF-SPECT.

The aim of this study was to assess the head-to-head accuracy of ^{18}F-FDG PET and CBF-SPECT in detecting AD among patients with cognitive impairment referred for scanning to assist diagnostic evaluation. To improve

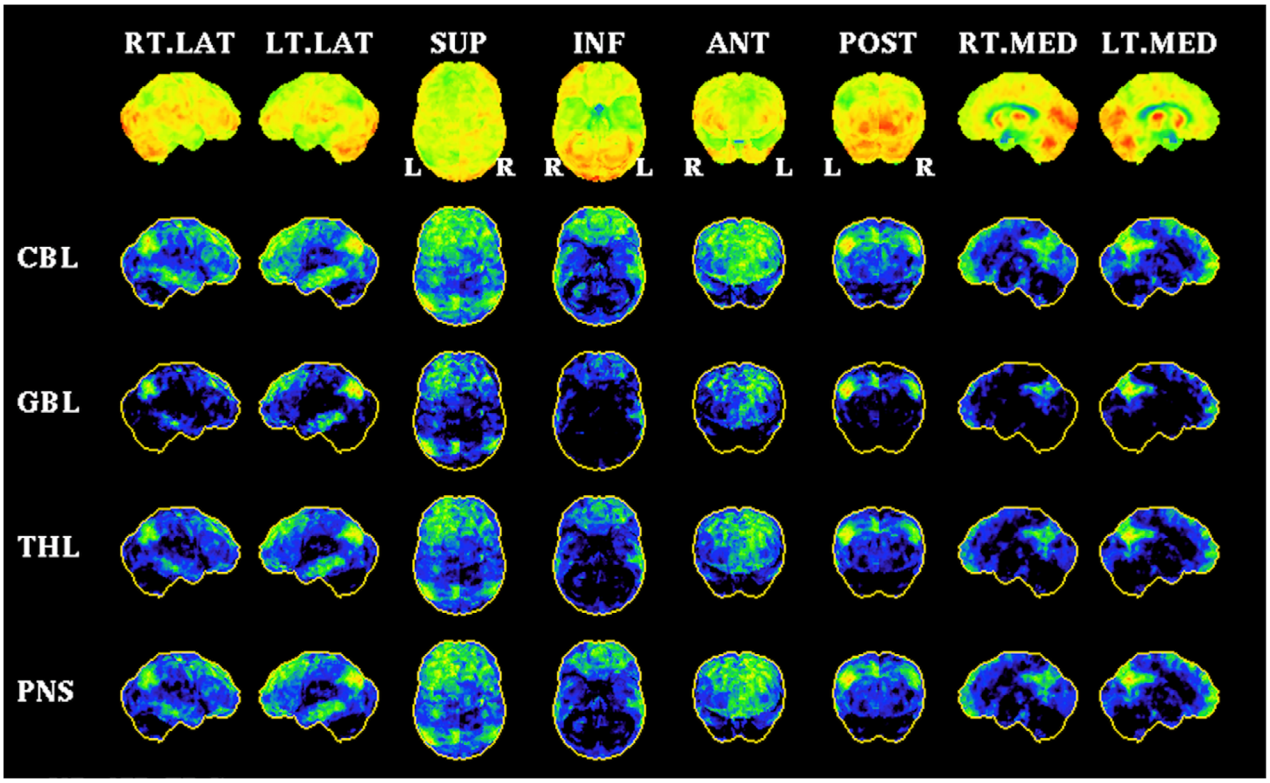

Figure 1 Neurostat 3D-SSP analysis of an ^{18}F-fluoro-2-deoxyglucose positron emission tomography study. Areas of regional hypometabolism >2 standard deviations below the normal database are represented in green. In this example, Neurostat 3D-SSP demonstrates metabolic changes typical of Alzheimer disease, including regional hypometabolism in the posterior cingulate, posterior parietal lobes (including precunei), lateral temporal and bilateral frontal lobes.

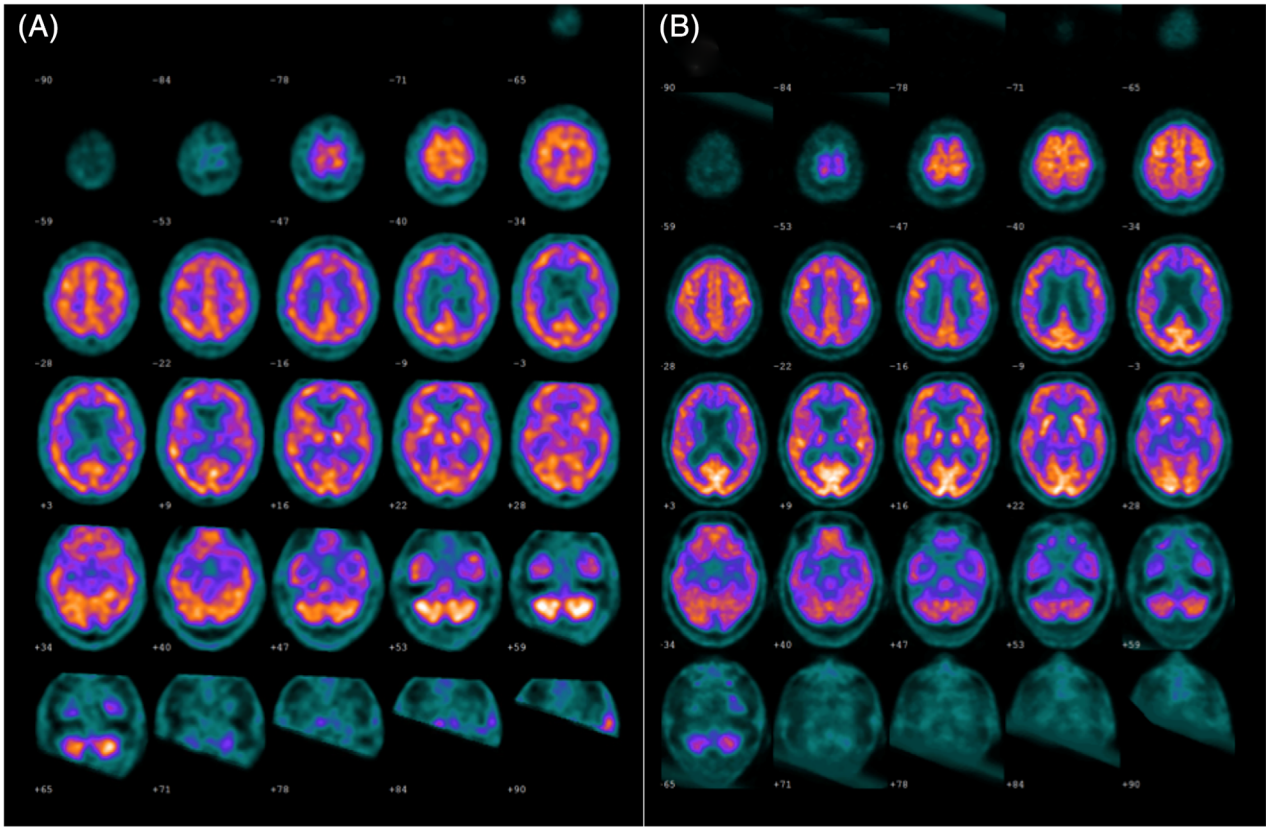

Figure 2 Transaxial slices from a cerebral blood flow-single-photon emission computed tomography (CBF-SPECT) (A) and ^{18}F-fluoro-2-deoxyglucose positron emission tomography (^{18}F-FDG PET) study (B) acquired from the same patient, demonstrating the superior resolution and image characteristics of ^{18}F-FDG PET. In this example, the significant parietal abnormalities (left > right) are much better appreciated on ^{18}F-FDG PET than CBF-SPECT.

the accuracy of the reference standard diagnosis we only used patients who had β-amyloid PET validated diagnosis. We hypothesised that ^{18}F-FDG PET would show superior diagnostic accuracy for AD compared to CBF-SPECT and provide greater reader confidence.

Methods

Study design and population

This was a retrospective study of a convenience population using data from patients clinically referred by memory disorder specialists to the Nuclear Medicine Department of Austin Health for the assessment of cognitive impairment. All patients who had both a CBF-SPECT and ^{18}F-FDG PET scans within a 12-month period and subsequently completed β-amyloid PET through participation in research studies prior to late 2015 (n = 126) were included. Three prospective phase III clinical trials have shown that visual reading of β-amyloid PET has 90% accuracy for neuropathological AD[17–19] so amyloid PET was required in this study to establish the reference standard as per international recommendations.[7] Patient demographics and clinical details (Table 1) were obtained from clinical notes including the imaging referral form, which required clinicians to select their current working diagnosis. The study was approved by the Austin Health Human Research Ethics Committee in accordance with the ethical standards laid down in the Declaration of Helsinki (as revised in Brazil 2013).

CBF-SPECT and ^{18}F-FDG PET studies

CBF-SPECT and ^{18}F-FDG PET studies were completed in a single tertiary centre (Austin Health) between November 2008 and October 2015. CBF-SPECT was performed first, with ^{18}F-FDG PET performed a median of 92 days later. Seventeen patients with diagnostic CBF-SPECT studies and subsequent amyloid PET did not undergo ^{18}F-FDG PET. These patients were added to the primary cohort for 'intention to treat' analysis (n = 143; Table 2).

Table 1 Demographics and clinical details of the patient cohort

Patient characteristics	No. patients (% of cohort)
Age (years)	
<60	20 (15.9)
60–69	47 (37.3)
70–79	45 (35.7)
>80	14 (11.1)
Gender	
Male	65 (51.5)
Female	61 (48.5)
Diabetes	
Insulin dependent	3 (2.3)
Non-insulin dependent	10 (7.9)
Referral diagnosis	
Mild cognitive impairment	70 (55.6)
Dementia	51 (40.5)
Primary progressive aphasia	5 (3.9)
β-Amyloid deposition on positron emission tomography	
Negative	35 (27.8)
Positive	91 (72.2)

CBF-SPECT was performed with either ^{99m}Tc-ECD (bicisate, $n = 105$) or ^{99m}Tc-HMPAO (exametazime, $n = 21$). An average of 719 MBq (range: 522–802 MBq) was administered with the patient resting in a quiet room with eyes closed. Images were acquired with one of three multihead SPECT cameras: Philips Brightview, IRIX (Philips Medical Systems, USA) or Symbia T16 (Siemens Medical Solutions, USA). Iterative reconstruction was performed using the ordered subset expectation maximisation algorithm. Following Chang attenuation correction, images were displayed in the anterior commissure posterior commissure (AC-PC) plane.

^{18}F-FDG PET was performed using an average of 254 MBq of ^{18}F-FDG (range: 180–318 MBq) following a 6-h fast. The average blood sugar level (BSL) at time of ^{18}F-FDG injection was 6.3 mmol/L (range: 3.3–-12.9 mmol/L). Images were acquired an average of 40 min (range: 27–62 min) following injection under resting conditions in a darkened room with eyes open. Images were acquired with the Gemini TF64, Ingenuity TF128 or Allegro PET cameras (Philips Medical Systems, USA). Computed tomography or transmission attenuation correction was applied. Acquisition was 10 or 15 min with a 256 × 256 matrix and 2 mm slices.

Neurostat 3D-SSP display was generated using the software supplied by Satoshi Minoshima.[20] This programme generates a *Z*-score semi-quantitative brain surface display of regional perfusion or metabolism compared to a database of healthy age-matched controls (Fig. 1).

Scan review

CBF-SPECT and ^{18}F-FDG PET images were reviewed by five nuclear medicine clinicians drawn from three major public hospitals in Melbourne, Australia. One operator reviewed the data set twice for the assessment of intra-operator reliability (the two reviews separated by 30 days). Reviewers had variable experience reading CBF-SPECT and ^{18}F-FDG PET ranging from a nuclear medicine trainee to a clinical professor in dementia imaging. Clinicians were blinded to all patient clinical information and to scan type. Scans were graded after combined review of transaxial slice (examples are shown in Fig. 2) and Neurostat 3D-SSP save screens. Reviewers selected a most likely diagnosis from six possible categories: AD, mixed AD and vascular dementia (VaD) (AD + VaD), DLB, VaD, fronto-temporal dementia (FTD) and normal. The first three categories (AD, AD + VaD and DLB) were grouped as AD to allow dichotomous analysis of AD versus non-AD with the latter including VaD, FTD and normal. DLB was included in the AD category as the CBF/metabolic pattern is largely indistinguishable, overlap with AD pathology is common[21] and the disorder is too infrequent for meaningful separate analysis in a cohort of this size. Reviewers graded their clinical confidence in the selected diagnosis, ranging from 0% (no confidence) to 100% (full confidence). Reviewers also graded the severity of regional cortical hypoperfusion/hypometabolism in five areas (Table 3): 0 if normal or 1 (mild), 2 (moderate) and 3 (severe).

The reference standard for accuracy analyses was final diagnosis dichotomised as either AD or non-AD. This

Table 2 Relative performance of cerebral blood flow-single-photon emission computed tomography (CBF-SPECT) and ^{18}F-fluoro-2-deoxyglucose positron emission tomography (^{18}F-FDG PET) in identifying Alzheimer disease (AD) from non-AD

	CBF-SPECT (n = 143)	^{18}F-FDG PET (n = 126)	Significance of difference (P-value)
Accuracy	54.0% (95% CI: 45–62%)	75.4% (95% CI: 67–82%)	0.0001
Sensitivity	42.9% (95% CI: 33–53%)	75.8% (95% CI: 66–84%)	0.0001
Specificity	82.9% (95% CI: 67–92%)	74.3% (95% CI: 58–86%)	0.45
Positive predictive value	86.7% (95% CI: 74–94%)	88.5% (95% CI: 79–94%)	0.78
Negative predictive value	35.8% (95%CI: 24–50%)	54.2% (95%CI: 40–67%)	0.045

CI, confidence interval.

Table 3 Regional hypoperfusion/hypometabolism among patients with positive amyloid positron emission tomography

	CBF-SPECT: average perfusion reduction*	^{18}F-FDG PET: average metabolic reduction*	Significance of difference (*P*-value)
Frontal	0.51	0.78	0.002
Anterior temporal	0.39	0.21	0.02
Lateral temporal	0.59	0.80	0.02
Parietal	0.70	1.10	<0.001
Posterior cingulate	0.64	0.86	0.01

This represents the average reduction in regional cerebral perfusion/metabolism identified on CBF-SPECT and 18F-FDG PET respectively. Reductions were qualitatively graded 0 (normal), 1 (mild), 2 (moderate) or 3 (severe). CBF-SPECT, cerebral blood flow-single-photon emission computed tomography; ^{18}F-FDG PET, ^{18}F-fluoro-2-deoxyglucose positron emission tomography.

diagnosis was obtained from the patients' research and clinical files in July 2019 and incorporated the β-amyloid PET result. All the patients with a negative β-amyloid scan had been classified as non-AD while all patients with a positive scan had a diagnosis of AD. There were three final diagnoses of DLB, all were β-amyloid scan negative and these were given a reference standard classification of non-AD. All patients had the β-amyloid PET as part of an observational research study with a median of 185 days elapsed from the ^{18}F-FDG PET. Amyloid tracers used included Pittsburgh compound B, florbetapir, florbetaben, flutemetamol and NAV4694. Amyloid PET results were classified as 'negative' or 'positive' using established visual methods by an expert reader blind to other data.

Statistical analyses

Statistical analyses were performed using GraphPad Prism and JMP software. The study's primary outcome was the accuracy in differentiating AD from non-AD using final diagnosis derived from clinical findings and β-amyloid PET as the diagnostic reference. Combined overall accuracy was assessed using the majority read of five reviewers. Sensitivity, specificity, positive predictive value and negative predictive value were calculated using standard methods. Differences in sensitivity and specificity were assessed using McNemar and chi-square paired analyses. Fleiss kappa was used to assess intra-operator and inter-operator reliability. Difference in reviewer confidence was assessed using the Student *t*-test and McNemar–Bowker test of symmetry.

Results

Patient clinical information

Median age was 69 years with a range from 50 to 84 years. Slightly more patients had mild cognitive impairment (MCI) (55.6%) than dementia (44.4%). Cerebral β-amyloid deposition was present in 72.2% of patients. Cohort characteristics are listed in Table 1.

Accuracy

All five operators showed individually higher accuracy in differentiating AD from non-AD using ^{18}F-FDG PET than with CBF-SPECT (Fig. 3). The combined overall accuracy based on the majority read was significantly higher for ^{18}F-FDG PET compared to CBF-SPECT (area under the receiver operating characteristic curve (AUROC) = 0.71 vs 0.61, $P = 0.02$). This difference in accuracy appeared to be equally present among patients with MCI (^{18}F-FDG PET = 68.6% vs CBF-SPECT = 50.0%, $P = 0.02$) and dementia (^{18}F-FDG PET = 81.4% vs CBF-SPECT = 65.1%, $P = 0.10$). When the additional 17 patients who completed CBF-SPECT but not ^{18}F-FDG PET were included, the significance of the difference in AUROC was unchanged. ^{18}F-FDG PET

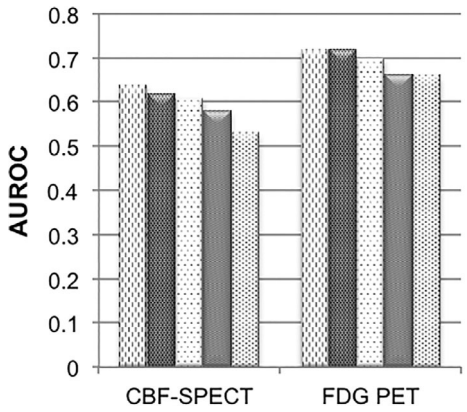

Figure 3 Individual reviewer accuracy in diagnosing Alzheimer disease using cerebral blood flow-single-photon emission computed tomography (CBF-SPECT) and ^{18}F-fluoro-2-deoxyglucose positron emission tomography (^{18}F-FDG PET); all five reviewers showed significantly higher area under the receiver operating characteristic curve with ^{18}F-FDG PET. Left to right: (▨), Reviewer 1 ($P = 0.04$); (■), Reviewer 2 ($P = 0.005$); (▨), Reviewer 3 ($P = 0.001$); (■), Reviewer 4 ($P = 0.001$); (▨), Reviewer 5 ($P = 0.001$).

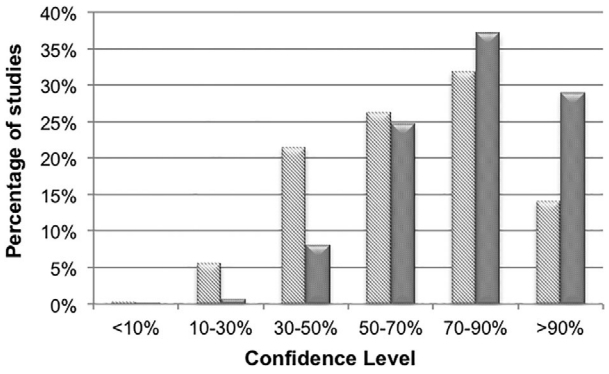

Figure 4 Reviewer confidence in selecting a primary diagnosis with cerebral blood flow-single-photon emission computed tomography (CBF-SPECT) (▨) compared to ^{18}F-fluoro-2-deoxyglucose positron emission tomography (18F-FDG PET) (▩).

showed considerably higher sensitivity (75.8% vs 42.9%, $P = 0.0001$, Table 2). The specificity was not significantly different between ^{18}F-FDG PET (74.3%) and CBF-SPECT (82.9%) ($P = 0.45$).

Reviewer confidence

Reviewers had greater confidence in selecting a primary diagnosis with ^{18}F-FDG PET than CBF-SPECT (Fig. 4), with an average confidence level of 75.5% versus 64.6% respectively ($P < 0.001$). Similarly, reviewers reported high confidence in differentiating AD from other diagnoses in 83.1% of ^{18}F-FDG PET studies compared to 67.2% for CBF-SPECT ($P = 0.001$).

Reproducibility

^{18}F-FDG PET showed high intra-operator reliability, with a kappa statistic of 0.79 (agreement = 91.3%) similar to 0.70 (agreement = 85.0%) for CBF-SPECT ($P = 0.12$). The inter-operator reliability of ^{18}F-FDG PET (kappa = 0.48, agreement = 75.4%) was also similar to CBF-SPECT (kappa = 0.43, agreement = 73.2%, $P = 0.49$).

Regional metabolic/perfusion reduction

Among patients with a positive β-amyloid scan, reviewers identified greater regional reductions in metabolism on ^{18}F-FDG PET than perfusion on CBF-SPECT (Table 3). These metabolic changes were observed in areas typically associated with AD, including the posterior cingulate, posterior parietal, lateral temporal and frontal lobes.[22] Although CBF-SPECT frequently showed hypoperfusion in the anterior temporal lobes, hypoperfusion in this area is not a characteristic feature of AD.

Discussion

Our study represents the largest head-to-head comparison to date of ^{18}F-FDG PET and CBF-SPECT in the assessment of dementia and was performed in the clinically relevant population of persons undergoing diagnostic work-up by memory disorders specialists after initial evaluation. ^{18}F-FDG PET showed markedly superior sensitivity in identifying patients with AD (75.8% vs 42.9%, $P = 0.0001$). ^{18}F-FDG PET was found to be superior on almost all assessed performance measures including accuracy, sensitivity and reviewer confidence.

On the primary outcome of accuracy, ^{18}F-FDG PET showed an overall AUROC of 0.71 compared to 0.61 for CBF-SPECT. This difference in accuracy was both clinically and statistically ($P = 0.02$) significant and was observed across all five reviewers irrespective of clinical experience. Our primary finding is consistent with the large body of non-comparative evidence, with meta-analysis finding in favour of ^{18}F-FDG PET.[8]

Our study represents a 'real world' comparison among patients clinically referred for the assessment of cognitive impairment. This feature is relatively unique to our study, with the majority of published papers assessing accuracy between highly selected groups of patients with well-established dementia diagnoses and healthy controls. Only two small studies have directly compared CBF-SPECT and ^{18}F-FDG PET among the true target population of patients clinically referred for the assessment of dementia.[10,11] These studies had a combined total of 79 patients. Although both showed approximately 20% greater sensitivity for ^{18}F-FDG PET, with similar specificity, one failed to detect a difference in accuracy between the two imaging technologies due to inadequate power. Our results, therefore, provide the most robust head-to-head confirmation of ^{18}F-FDG PET's superiority among a clinically referred cohort of patients and this study is the first head-to-head study to use a pathology biomarker assisted reference standard diagnosis that has accuracy similar to post-mortem neuropathological diagnosis for AD.

While the relative difference in accuracy of ^{18}F-FDG PET and CBF-SPECT is consistent with existing literature, the absolute accuracies observed in our study are lower than commonly reported. This observation is likely multifactorial. Our patients were clinically referred after expert clinical assessment so likely to have mixed clinical features and underlying mixed pathology. Over half of our cohort had MCI which is associated with more subtle functional change on CBF-SPECT and ^{18}F-FDG PET than seen with dementia.[23] When dementia was present, ^{18}F-

FDG PET had accuracy of 81% compared to 67% in MCI. The inclusion of patients with DLBs is likely to reduce specificity as this disorder is associated with highly variable amyloid deposition[21] and a pattern of hypoperfusion/hypometabolism similar to AD. This study had three patients with final clinical diagnosis of DLB, all β-amyloid PET negative and each had a reference standard diagnosis of non-AD. However, reanalysis of the study after exclusion of these DLB patients had no significant effect on the accuracy of CBF-SPECT and ^{18}F-FDG PET for diagnosis of AD. Finally 11% of the patients were aged over 80 years. In the very elderly, limbic-predominant age-related TDP-43 encephalopathy (LATE), a condition that includes primary hippocampal sclerosis, is a frequent cause of amnestic decline that mimics AD.[24] These patients may be amyloid negative but show reduced CBF and metabolism in the posterior cingulate and precuneus similar to mild AD and therefore such cases may also reduce the specificity of CBF SPECT and ^{18}F-FDG PET for detection of AD. Of note, it has been recently reported that a higher ratio of inferior to medial temporal lobe metabolism on ^{18}F-FDG PET may distinguish LATE from AD.[22]

Limitations of the study include the relatively small proportion of non-AD patients, which may have prevented finite conclusions being drawn regarding the relative specificity of the two technologies. Also the scans were not performed concurrently but the time interval between scans is unlikely to have significantly impacted our findings. The median interval of 3 months between CBF-SPECT and ^{18}F-FDG PET represents a short fraction of the natural history of AD.[25] To address this we examined studies performed within 1 month and found a similar magnitude of superiority in sensitivity for ^{18}F-FDG PET. β-amyloid deposition is a similarly slow process, with amyloid PET measures shown to progress by only 2–3% per year.[26] The median 185 days difference between amyloid PET and SPECT/FDG PET studies is therefore also unlikely to impact on results.

Conclusions

In a 'real-world' cohort, head-to-head comparison study, ^{18}F-FDG PET was found superior to CBF-SPECT in the diagnosis of AD. ^{18}F-FDG PET showed significantly higher accuracy and sensitivity with greater reader confidence and therefore should be performed in clinical practice in preference to CBF-SPECT.

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