European Journal of Radiology 94 (2017) 16–24

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Review

The diagnostic value of FDG and amyloid PET in Alzheimer's disease—A systematic review

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ARTICLE INFO

Keywords:
Alzheimer's
Dementia
FDG
PET
Amyloid

ABSTRACT

Purpose: By 2050 it is projected that 115 million people worldwide will have Alzheimer's Disease (AD) [1]. Recent attempts have been made to redefine the diagnostic criteria of AD to include markers of neurodegeneration – measurable by FDG-PET – and markers of amyloid accumulation – measurable by amyloid-PET.

Materials and methods: A systematic review of the literature was performed to examine the current diagnostic use of amyloid and FDG PET. MEDLINE and EMBASE databases and the Cochrane Database were searched for relevant papers

Results and discussion: This search resulted in twenty-nine papers on amyloid imaging, twenty-three papers on FDG-PET and eight papers which utilized both techniques. Both modalities are considered in turn with regards to their diagnostic accuracy, their role in mild cognitive impairment (MCI) and prognostication, their use in the differential diagnosis of AD and their clinical application. As evidenced from the current literature, both amyloid and FDG-PET meet criteria for suitable biomarkers for the diagnosis of AD. They both indicate pathophysiological processes, albeit at different stages of the Alzheimer's process, and are distinct from normal patterns of aging.

Conclusion: Both techniques have been shown to detect AD with high sensitivity and specificity compared to other neurodegenerative processes and cognitively normal age-matched individuals. However, future studies with standardised, uniform thresholds and a lengthier longitudinal follow-up need to be conducted to allow us to make surer conclusions about the future role of PET in clinical practice. In addition, comparison with post-mortem diagnosis, rather than clinical diagnosis with its acknowledged flaws, would result in more powerful statistical outcomes – which is becoming increasingly important given that several disease-modifying AD drugs are now in phase 3 trials.

1. Introduction

By 2050 it is projected that 115 million people worldwide will have Alzheimer's Disease (AD) [1]. AD is a progressive neurodegenerative disorder, characterized clinically by decreasing cognition, worsening episodic memory and increasing difficulty with activities of daily living. Pathologically it is defined by the presence of β-amyloid plaques and neurofibrillary tangles of hyperphosphorylated tau on autopsy [2]. Given the expected increasing global burden it is critical that AD is diagnosed with a high degree of accuracy –for the purposes of conducting significant clinical trials, for resource and service provision planning, and, on an individual level, ensuring the right diagnosis so that appropriate management can take place.

Until relatively recently, the clinical community relied on the *National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association* (NINDS-ADRDA) criteria to diagnose patients with 'probable' dementia [3]. These diagnostic criteria meant that dementia could only be diagnosed retrospectively – when the threshold of AD had been crossed – and definite diagnosis could only be confirmed post-mortem [4].

Our gold-standard diagnostic test continues to be histopathological examination at autopsy [4]. However scientific advances in relation to our knowledge of genetic markers, neuroimaging biomarkers and markers of neurodegeneration mean that it is now possible to identify AD in its 'prodromal' stage. Our increased knowledge of the pathological processes behind AD has led to attempts to redefine the diagnostic criteria in order to include markers of amyloid accumulation, and markers of neurodegeneration [5,6]. Two such modalities include amyloid-PET and FDG PET.

2. Materials and methods

2.1. Search strategy and selection

Multiple databases were searched to identify appropriate papers for

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http://dx.doi.org/10.1016/j.ejrad.2017.07.014
Received 2 May 2017; Received in revised form 13 June 2017; Accepted 17 July 2017

the review according to the PRISMA guidelines [7]. Targeted searches were performed for each imaging technique using Medline, EMBASE, Google Scholar and the Cochrane library using appropriate keywords; 'amyloid-PET'; 'Pittsburgh Compound B'; 'FDG-PET' and 'Alzheimer's Disease'; including MeSH terms/synonyms to ensure that no relevant papers were missed.

2.2. Inclusion/Exclusion criteria

Given that the use of imaging biomarkers in AD is a relatively recent and evolving area, the search was restricted to clinical trials within the last 15 years (2001–16). The search was also limited to those papers published in peer-reviewed scientific journals. Articles which focused on drug trials were excluded, as were those which focused solely on other forms of dementia. Several articles were found to have reviewed the same population/imaging database – in this case the most recent article was included.

2.3. Preliminary reading and refinement

Using the search methods detailed above led to a total of 2158 papers looking at FDG and amyloid-PET in AD. Initial reading of abstracts and removal of duplicate papers, and those papers which did not fit the inclusion criteria resulted in 78 papers looking at the use of FDG-PET in AD and 83 papers looking at amyloid imaging in AD. Those studies which assessed the same patient cohort were eliminated (aside from the most recent and/or most influential), as were papers which focused on imaging software. The end result of this process left 29 papers on amyloid imaging, 23 papers on FDG-PET and 8 papers which utilized both techniques (Tables 1–3).

3. Results and discussion

3.1. Amyloid-PET

The first major paper to look at amyloid imaging in AD was published in 2004 [8] using the radiotracer *N*-methyl-[^{11}C]2-(4′-methylaminophenyl)-6-hydroxybenzothiazole – more commonly referred to as Pittsburgh Compound B (PIB). PIB is a radioactive analogue of thioflavin T, traditionally used in histopathology. This radioligand readily crosses the blood-brain barrier and binds to amyloid plaques with high affinity – specifically insoluble fibrillary forms of amyloid-beta 40 and 42 [9] (Fig 1-2).

Since the development of PIB, several other radioligands have been developed which also bind to amyloid plaque. ^{18}F-florbetapir was FDA approved in 2012, followed by ^{18}F-flutemetamol and ^{18}F-florbetaben. The development of these compounds was necessitated by the short half-life of PIB (20 min) meaning it had to be developed on site and was therefore limited to large research centres which had a cyclotron. The newer ^{18}F-labelled tracers have half-lives of 110 min and their initial trials demonstrated similar efficacy to PIB.

When interpreting PIB images, the cerebellar grey matter has been used as a reference, given that it typically has little amyloid plaque compared to the cortex. Where there are numerous plaques within the cerebellum, the pons is used as an alternative reference region (e.g. advanced AD, familial AD). The distribution volume ratio (DVR) is used by several studies; this is the ratio of amyloid radioligand volume in a specified region of interest (ROI) to the distribution of the radioligand in the cerebellum. Alternatively, the standardised uptake value ratio (SUVR) is used which measures the activity in the neocortical ROI to determine plaque density, adjusted for weight, surface area and dosage of amyloid ligand administered [10].

3.1.1. Diagnostic accuracy

Earlier studies on Amyloid-PET imaging compared amyloid-PET findings to clinical symptoms and cognitive assessments (Table 1). A 2004 study reported on 16 clinically diagnosed 'probable' AD patients in the Karolinska Institute, Stockholm [8]. This group found a significant difference in the amyloid deposition patterns seen in AD patients compared to healthy controls (HC). Their imaging findings of areas with significantly high amyloid deposition matched those areas known to be susceptible to plaque deposition in AD post-mortem [11] [12]. They found a significant increase in amyloid retention in the frontal cortex of the AD group (1.94-fold, $p = 0.0001$), and large increases in the parietal, occipital and temporal cortices. A subsequent longitudinal follow up study of the 16 AD patients rescanned them at 2 years [13]. They found no significant difference in PIB retention at 2 years compared to baseline, despite an overall decrease in MMSE – with 5 of the patients showing a significant decrease in their MMSE score of > 3 ($p < 0.01$). The authors postulated that patients with AD have reached a plateau by the time they exhibit clinical symptoms, thereby suggesting that amyloid deposition precedes the onset of cognitive decline. However, it is important to note that all of the 16 patients were on cholinesterase inhibitors and an additional 5 were also on memantine (NMDA antagonist). Their cognitive assessment of patients also relied heavily on the MMSE which has limited testing of visual or personal memory and does not test executive function, all of which are key impairments in AD.

Table 1
Reported accuracy of amyloid and FDG-PET for the diagnosis of AD.

Reference	Population	Outcome measure	Sensitivity & Specificity (plus confidence intervals, where stated)
[82]	81 AD 69 HC	Ability of amyloid PET (florbetaben) to distinguish between probable AD vs HC	Sensitivity: 80% (95% CI 71–89) Specificity: 91% (95% CI 84–98)
[83]	13 AD 12 MCI 21 HC	Ability of amyloid PET (florbetapir) to distinguish between probable AD vs HC in routine clinical environment	Sensitivity: 84.6% (95% CI 0.55–0.98) Specificity: 38.1% (95% CI 0.18–0.62)
[16]	69 terminally ill patients	Comparison of amyloid PET (flutemetamol) results to post-mortem histology	Sensitivity: 86% (95% CI 72–95%) Specificity: 92% (95% CI 74–99%)
[84]	27 AD 20 MCI 20 HC	Compared amyloid PET (flutemetamol) results to clinical diagnosis as standard of truth	Sensitivity: 93.1% Specificity: 93.3%
[51]	30 AD 20 MCI 32 HC 11 FTLD 7 DLB 5 PD 4 VaD	Ability of amyloid PET (florbetaben) to identify clinically diagnosed AD	Sensitivity: 97% Specificity: 88% (with an AUC of 0.92)
[81]	ADNI: 89 AD 102 HC NESTP-DD: 237 AD 36 HC	Ability of FDG-PET to discriminate between AD and controls in two independent multicentre samples (NEST-DD and ADNI)	ADNI Sensitivity: 83% Specificity: 78% NEST-DD Sensitivity: 78% Specificity: 94%
[85]	11 AD 22 MCI 15 HC	Ability of FDG-PET to accurately identify AD/MCI vs HC	Sensitivity: 91% Specificity: 87%
[44]	199 AD 114 MCI 110 HC 98 FTLD 27 DLB	Ability of FDG-PET to distinguish AD from HC and other dementias	Sensitivity: 98% Specificity: 99% (98% accuracy $P < 0.001$)
[86]	38 AD 30 DLB 30 HC	Ability of FDG PET to detect clinically diagnosed AD	Sensitivity: 85% Specificity: 90%

AD – Alzheimer's Disease; MCI – Mild cognitive impairment; HC – Healthy control FTLD – Fronto-temporal lobe dementia; DLB – Dementia with Lewy body; VaD – Vascular dementia; PD – Parkinson's Disease.

Table 2
Reported accuracy of PET for prediction of conversion from MCI to AD.

Reference	Type of PET	ROI (± threshold for 'positivity')	Population	Follow-up duration	Rate of conversion/progression from MCI to AD
[17]	Amyloid (PIB)	10 ROIs (ROI to cerebellum ratio of > 1.6)	37 AD 21 MCI	33.3 ± 19.3 months	63.6% (7/11) of positive scans progressed (0/11 negative scans progressed)
[22]	Amyloid (PIB)	Global cortex (ROI to cerebellum ratio of > 1.5)	218 MCI	2 years	50% (82/164) of positive scans progressed (Amyloid positive subjects had a hazard ratio of 3.2, 95% CI 1.4–7.1, P = 0.004)
[21]	Amyloid (florbetaben)	Global cortex (ROI to cerebellum ratio of ≥1.45)	45 MCI	4 years	87.5% (21/24) of positive scans progressed (predictive accuracy of 94%, 95% CI 74%–99%)
[18]	Amyloid (PIB)	6 ROIs (ROI to cerebellum ratio ≥ 2 SD from control mean)	31 MCI 26 HC	2.68 years	82% (14/17) of positive scans progressed (1/14 negative scans progressed)
[87]	Amyloid (PIB)	11 ROIs (ROI to cerebellum ratio of > '1.5 × the interquartile range higher than the third quartile' – allowing for an intermediate range 2.5% above and below)	23 MCI	21.2 ± 16.0 months	38% (5/13) of positive scans progressed (0/10 negative scans progressed)
[53]	FDG	Temporo-parietal and posterior cingulate (CMRglu ratio of 1.138 in ROIs)	48 MCI 41 HC	12 months (range 12–27 months)	73.7% (14/19) of positive scans progressed (predicted progression with 92.9% sensitivity and 82.4% specificity)
[50]	FDG	Right temporo-parietal and posterior cingulate (SPM maps were thresholded at Z > 3.09)	17 MCI 15 HC	18 months	100% (7/7) with metabolism below threshold at right temporo-parietal region progressed 87.5% (7/8) with metabolism below threshold at post cingulate progressed
[54]	FDG	20 ROIs covering entire brain (CMRglu at Z-score of > 1.64)	30 MCI	16 months	84.6% (11/13) positive scans progressed (1/17 negative scans progress; reported sensitivity of 92%, specificity of 89%)
[55]	FDG	Parietal, posterior cingulate and temporal regions (z-score decrease by > 2 in more than 50 adjacent pixels)	16 MCI	19 months	57% (4/7) positive scans progressed (0/9 with negative scans)
[45]	FDG	Visual classification by nuclear medicine physician using a priori criteria	2 branches: - 146 MCI with clinical follow up - 138 MCI with histopathological diagnosis	Longitudinal follow-up: 3.2 years Autopsy: 2.9 years	91% (191/210) with positive scans progressed (15/74 with negative scans progressed)

AD – Alzheimer's Disease; MCI – Mild cognitive impairment; HC – Healthy control; ROI – Region of interest; CMRglu – Cerebral metabolic rate of glucose.

Table 3
Amyloid and FDG-PET findings in common neurodegenerative conditions.

Neurodegenerative condition	Amyloid PET findings	FDG-PET findings
AD	Diffuse cortical amyloid tracer binding, with predominance in frontal and posterior cingulate	Temporoparietal cortex, and posterior cingulate hypometabolism
FTLD	No significant PIB binding	Predominantly frontal and parieto-temporal hypometabolism
DLB	Heterogenous, but typically lower than seen in AD	Occipital cortex hypometabolism – particularly in the primary visual cortex
VaD	No significant PIB binding	Consensus unclear
PD	No significant PIB binding	Consensus unclear

AD – Alzheimer's Disease; FTLD – Fronto-temporal lobe dementia; DLB – Dementia with Lewy body; VaD – Vascular dementia; PD – Parkinson's Disease.

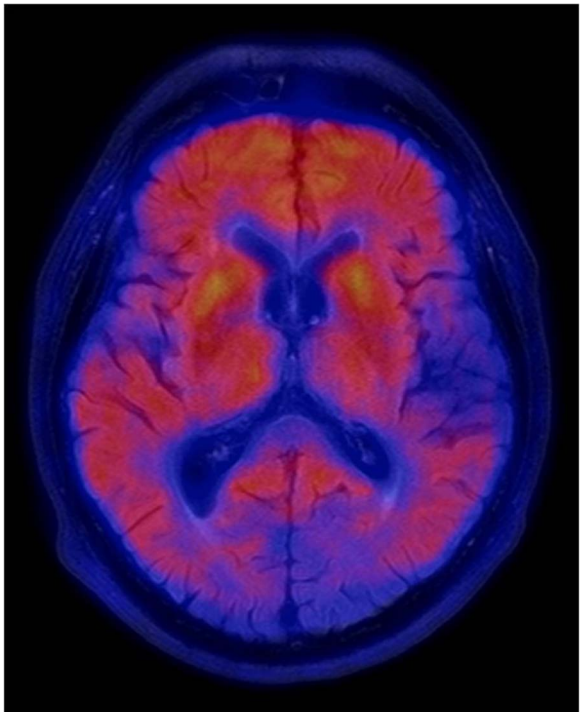

Fig. 1. Illustrative ^{11}C –PIB PET-MR image from a patient with Alzheimer's Disease demonstrating high tracer retention in the frontal lobes and in lesser extent on the parietal lobes and the lateral temporal cortex, worse on the right, along with striatal binding. Note the variable degree of binding, which does not correlate with the severity of dementia.

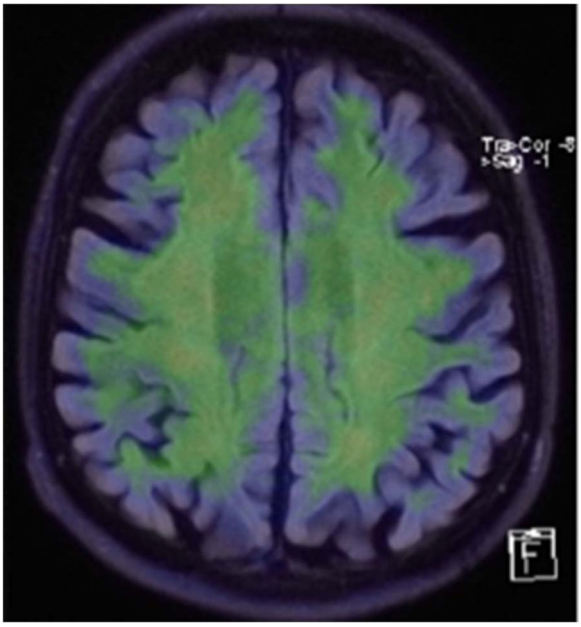

Fig. 2. Negative ^{11}C –PIB-PET-MR image from a patient with symptoms suggesting Alzheimer disease demonstrating a distinctive pattern of moderate degree non-specific tracer uptake within the white matter but not any cortical binding. The FLAIR-T2-weighted MR image demonstrates bilateral frontoparietal sulcal widening indicating cortical volume loss.

Several studies have looked at the correlation between amyloid-PET findings and the gold-standard –post-mortem histopathology [14]. One such paper [15] compared PIB retention levels in 10 patients who had all undergone a frontal cortical biopsy (for the purposes of intraventricular pressure monitoring as workup for normal-pressure hydrocephalus). All patients also underwent a thorough neuropsychological screening programme. The study found a direct correlation between individuals who had amyloid beta confirmed on biopsy, and amyloid levels seen in the frontal region on PIB-PET ($P < 0.05$) [15].

Trials examining the diagnostic accuracy of the 18-fluorine tracers included much larger cohorts of patients as part of phase 3 trials examining specificity and sensitivity. A *JAMA* multicentre trial from 2008 imaged 176 terminally ill patients using radioactive-labelled flutemetamol [16]. 69 patients died during the course of the study – their PET results were then compared to post mortem results. Authors reported a sensitivity of 86% (95% CI 72–95%) and a specificity of 92% (95% CI 74–99%). It must be acknowledged, however, that the 'end-of-life' status of these patients results in limitations on what we can infer from this study: the cohort examined was not characteristic of those who would typically present to a memory clinic, patients did not have MRIs to account for volume loss, and there was no element of formal neuropsychological testing.

3.1.2. Identifying MCI and prognostication

Much of the literature on amyloid-PET focuses on patients with mild cognitive impairment (MCI), as the common belief is that this is the stage in disease progression where meaningful intervention can be made (Table 2). Several studies have found correlations between patients with MCI who are PIB positive on PET and their rates of conversion to AD on follow-up [17–21]. The much-cited paper by Jack et al. [22] looked at data from 218 patients with MCI identified after thorough neuropsychological testing. Authors found that MCI patients identified as 'amyloid-positive' on PET were significantly more likely to convert to AD during the two year follow up compared to those MCI patients without PIB retention (50% vs 19%). However, when they looked at the 'amyloid positive' cohort in isolation they did not find that amyloid predicted a shorter time to progression ($p = 0.44$), whereas hippocampal atrophy identified on MRI did predict a significantly shorter time to progression ($p < 0.001$). The authors therefore recommend the use of both imaging modalities to aid in prognostication of progression to AD, combining the high sensitivity of hippocampal atrophy with the specificity of PIB-PET. An obvious limitation of this study, as with many other studies looking at MCI, is the relatively short follow-up time.

One study which attempts to address this issue [19], followed up the subjects for a mean of 10.8 years. This longitudinal study included 57 patients from the Baltimore Longitudinal Study of Aging (BLSA), 6 of whom had been diagnosed with MCI (using the clinical dementia rating

score). Patients had been followed-up via yearly cognitive assessment – given that PIB imaging was not available at the time of the study's conception, their long-term cognitive profile was compared with a later PIB-PET. They found that increased amyloid burden significantly correlated with longitudinal declines in verbal learning and memory, but not visual memory. Using a voxel based analysis, associations were most marked in frontal and lateral temporal regions.

However, several studies present conflicting evidence regarding the link between amyloid load, cognitive decline and prognosis [23,24]. One such study involved 177 patients, aged over 60 years, with no objective cognitive impairment who underwent PIB-PET as well as robust cognitive testing [25]. The authors reported that while patients with high PIB retention tended to have lower episodic memory scores than those with low/no PIB retention, there was not a significant effect on overall cognition. This lack of association between PIB retention and cognition, however, is at odds with the vast majority of the published literature. In those with objective memory impairment there is a higher probability of identifying high amyloid burden on PET [26,27], and a significant link between plaque burden and ongoing neurodegenerative pathology [28].

Clinically, Amyloid-PET's role in MCI is more of an exclusionary one, in that the presence of amyloid plaques are necessary, but not sufficient by themselves for development of AD. Therefore, given that up to 35% of cognitively normal older people have positive amyloid-PET results, it's power is limited by its moderate positive predictive value [29,30].

3.1.3. Differential diagnosis: distinguishing from other forms of dementia

Similarities in the initial clinical presentation of AD and other dementias has long been an issue with regards to accurate diagnoses [31]. Previous research has reported that anywhere between 10 and 40% of patients who are diagnosed clinically with frontotemporal lobar degeneration (FTLD) have AD on histopathology [32,33]. Given that FTLD is not linked pathologically to the presence of amyloid plaques it is therefore logical to attempt to differentiate the two via amyloid-PET. A cohort of 107 patients clinically diagnosed as AD (62 patients) or FTLD (45 patients) underwent both amyloid and FDG PET to ascertain each modality's ability to distinguish the two pathologies [34]. The study found that PIB-PET was both sensitive (89%) and specific (83%) at discriminating between the two disease processes. Given the numerous clinical trials and symptomatic treatments available for AD, clinicians typically want to ascertain diagnosis early in the disease course. PIB-PET therefore offers a valid means by which to do so with high sensitivity (Table 3).

Despite this clearly advantageous use of amyloid-PET, it has its shortcomings – dementia with Lewy Bodies (DLB) is the second most prevalent form of dementia after AD [35]. A 2014 study attempted to differentiate between the two forms of dementia using a combination of florbetapir and florbenazine (a marker of dopamine degeneration) [36]. Despite amyloid burden demonstrating significant correlation with cognitive status in DLB ($p = 0.046$), florbetapir was unable to distinguish with any reliability between AD and DLB.

3.1.4. Clinical application: safety, diagnostic confidence and economic viability

Pittsburgh Compound B is the most studied of all the tracers. From initial trials in the University of Pittsburgh it is known to easily cross the blood-brain barrier soon after injection, and is rapidly cleared, leaving no radiolabelled metabolites in the brain. [37]. The FDA approved 18-fluroine derivatives (florbetaben, florbetapir and flutemetamol) have all shown a similar safety profile to PIB – the most common side effects reported in phase three trials were injection site pain and reaction at the injection-site [10].

A 2013 trial [38] followed 154 memory clinic patients over a two-year period following their diagnosis of AD. Patients completed both PIB-PET and amyloid-PET shortly after diagnosis – authors then examined the effects of these results on clinical diagnosis and diagnostic confidence of patients' treating clinician. Looking at amyloid in isolation, diagnostic confidence changed from 71 ± 17% before imaging, to 87 ± 16% after imaging. This significant improvement is supportive of the use of amyloid-PET alongside expert clinical judgement.

Despite limited clinical application outside the research setting at present, evidence suggests that earlier diagnosis of AD and commencement of pharmacotherapy reduces societal costs [39,40]. A recent French study reported that despite the upfront costs associated with amyloid-PET, introduction of such a specific means of biomarker detection would affordably increase quality-adjusted life years [39]. One can also not underestimate the benefit to both patients and their families of obtaining a more certain diagnosis – an aspect highlighted by several independent qualitative analyses [41,42].

3.2. FDG PET

FDG-PET, as a measure of cerebral glucose metabolism, is a marker of neurodegeneration and is therefore useful in AD to detect characteristic regional hypometabolism. Previous studies on the pattern of regional cerebral glucose utilization (rCMRglu) in normal aging has shown that, in a group of 40 cognitively normal subjects, those over the age of 70 had a mean decrease in rCMRglu of 26% compared to those at age 18 [43] – particularly susceptible were the superior frontal and superior parietal cortices (Fig 3-4).

3.2.1. Diagnostic accuracy

Large multicentre studies have established a characteristic profile of rCMRglu in AD (Table 1). A 2008 trial employed an automated technique using voxel based comparisons to establish a specific, objective profile for AD [44]. They found that FDG PET could distinguish AD subjects from normal controls with 99% sensitivity and 98% specificity (98% accuracy, $p < 0.001$). Similarly, high sensitivities were demonstrated in an earlier trial [45] which performed FDG-PET in 284 patients and compared their findings to later post-mortem histopathological findings, carried out a mean of 2.9 years after the initial PET. Using a binary reporting system (AD positive/negative) authors found that FDG-PET diagnosed AD with a sensitivity of 94% and specificity of 73% when compared to the gold-standard of histopathology.

The specific pattern of hypometabolism in AD has been well studied. A relatively small study looking at 22 'difficult-to-diagnose' patients compared their FDG-PETs with eventual histopathology. They found bilateral temporo-parietal hypometabolism to be the characteristic pattern associated with pathologically confirmed AD [46]. A separate study points to medial temporal lobe as being the brain region first affected in AD, with a sensitivity of 90% in identifying AD [47]. Longitudinal imaging follow-up of patients with established AD found an ongoing decrease in FDG uptake as the disease progresses, with particularly notable neurodegeneration in the frontal, lateral temporal and parietal lobes. [48]. Authors in this study of 8 AD patients found a correlation between FDG uptake and MMSE changes ($\rho = 0.54$, $p < 0.01$), although their results are limited by the small sample size.

3.2.2. Identifying MCI and prognostication

Early studies regarding the use of FDG-PET to identify 'prodromal' or 'preclinical' AD involved relatively small numbers of patients (Table 2). A longitudinal study on 20 MCI patients was carried out to determine cerebral metabolic characteristics of those who converted to AD [49]. Patients underwent FDG-PET at the beginning of the investigation and at follow-up as well as a battery of neuropsychological tests. Patients were followed up for a mean of 35.5months, after which time authors categorised them as 'progressive MCI' ($n = 9$), if they met diagnostic criteria for AD, or 'stable MCI' ($n = 11$) based on their repeat PET/cognitive results. Despite not referencing exactly which criteria they used to diagnose AD the authors found that the brain region which most reliably predicted progression to AD was the left temporo-parietal

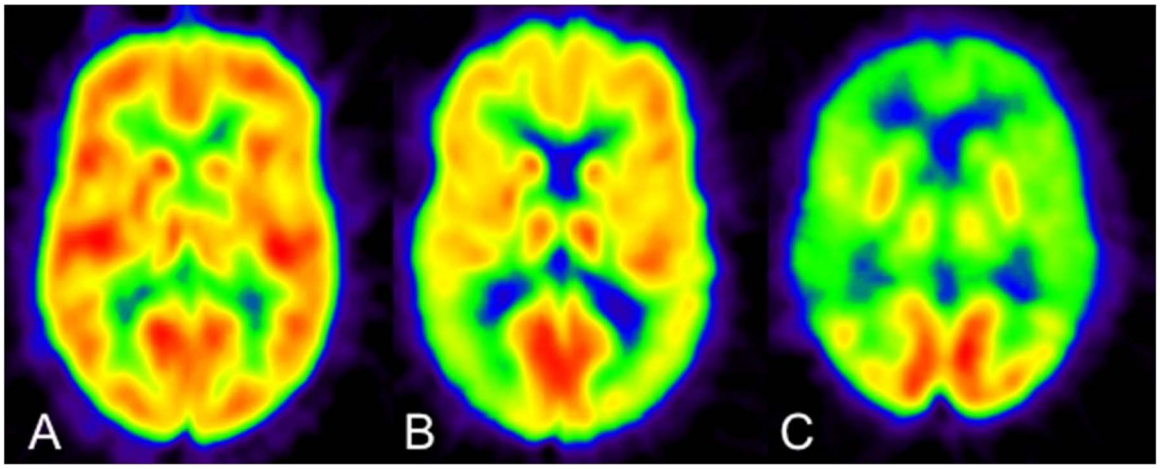

Fig. 3. (A) FDG-PET of a cognitively normal subject; (B) of a patient with suspected early Alzheimer's Disease (C); and of a patient with advanced Alzheimer's disease. Expected distribution pattern of avid cortical FDG uptake on the grey matter, the basal ganglia, and the thalami is seen in the healthy subject. The patient with MCI demonstrates widespread obvious reduction in the parietal (more pronounced) and secondarily in the frontotemporal and basal ganglia glucose metabolism; the findings are worse on the right side. The regional cerebral metabolic rate of glucose is severely impaired on the patient with advanced Alzheimer's disease with residual tracer activity on the thalami and basal ganglia. The occipital cortex retains its physiological glucose metabolism in Alzheimer's disease, unlike in dementia with Lewy bodies.

area. They stated that metabolism in this area, combined with performance in visuospatial testing gave a 90% correct classification of future prognosis. Conflicting results were produced in a 2003 study which determined that reduced right temporo-parietal FDG uptake was a marker of rapid conversion to AD ($p = 0.02$) [50]. Two further papers with similar sample sizes emphasise the potential role of FDG in predicting which MCI patient will eventually develop AD, with consistent overlap in the regions most affected – inferior parietal [51] cortex [52] and inferior parietal and medial temporal cortex [53].

Using FDG-PET in combination with other proven biomarkers of AD to predict prognosis in MCI has had success in the literature. A combination of APOEpsilon4-positive genotype and FDG-PET was used to risk stratify patients into 'high' or 'low' risk for conversion to AD [54]. In their study of 40 patients with a diagnosis of MCI the combination of genotyping and imaging was very specific for early diagnosis of AD (100%). However, FDG-PET alone had high sensitivity (92%) and specificity (89%) in predicting clinical outcome for those patients with MCI. A subsequent paper [55] attempted to further improve the prognostic accuracy of FDG-PET via combination with CSF measures of phospho-tau. During their 19month follow-up of 16 MCI patients they found that a pathological FDG-PET and elevated phospho-tau levels accurately predicted deterioration but there was little improvement in predicting conversion compared to FDG-PET alone.

3.2.3. *Differential diagnosis: differentiating from other forms of dementia*

As previously mentioned, amyloid-PET is of benefit in situations where the underlying pathophysiology differs (e.g. FTLD) but is of limited use where there is pathological overlap (DLB) (Table 3). A 2001 study compared the FDG-PET images of 11 histologically confirmed DLB patients to those of 10 confirmed AD patients [56]. They reported that although there was significant overlap between metabolic patterns in both groups (parietotemporal, posterior cingulate) only the DLB

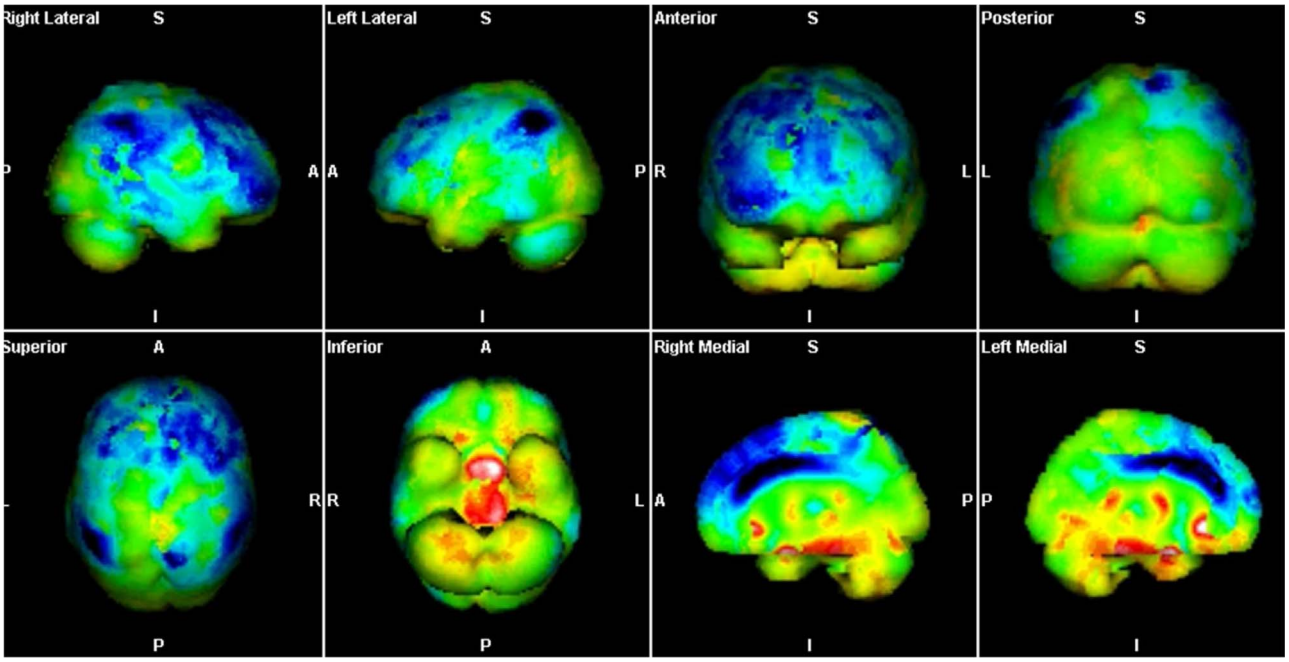

Fig. 4. 3-Dimensional stereotactic surface projection (3D-SSP) results showing the spatial distribution of FDG hypometabolism in AD – again demonstrating the residual tracer activity on the thalami and basal ganglia.

group were found to have significant hypometabolism in the occipital cortex, most notable in the primary visual cortex, which distinguished DLB from AD with 90% sensitivity and 80% specificity. The second arm of this study followed a group of 53 patents who met the clinical criteria for 'probable' AD – 13 of these patients were found to have DLB at autopsy, all of whom demonstrated a significantly reduced cerebral metabolism in the primary visual cortex in their earlier FDG-PETs. These findings were reproduced in a 2005 study which included 25 AD patients, 20 DLB patients and 19 healthy controls [57]. Authors found a significant reduction in rCMRglu in Brodmann areas 17 (V1–primary visual cortex), 18 and 19 (visual association area).

FDG has been shown to differentiate between AD vs FTLD with greater accuracy than clinical assessment [58]. The study presented 6 dementia experts with 45 patients with either pathologically confirmed AD (n = 31) or FTLD (n = 14) and compared their clinical diagnosis to visual interpretation of FDG-PET scans. FDG-PET reading was found to have greater diagnostic accuracy than their initial clinical assessment (89.6%), and had greater inter-expert reliability (kappa = 0.78).

3.2.4. Clinical application – safety, diagnostic confidence and economic viability

Despite the widespread use of FDG-PET in a multitude of other areas in clinical medicine, particularly in oncology, there have been no safety issues raised in the literature.

Given that dementia can typically begin with subtle symptoms, diagnosing patients early can prove a challenge for clinicians. A retrospective study [59] focused on 94 memory clinic patients with a difficult or unclear dementia diagnosis. Use of FDG-PET by their treating clinicians assisted in lowering the number of uncertain diagnoses from 39% to 16%. At 18-month follow-up, the result of FDG-PET had led to a change in diagnosis in almost a third of the 94 patients. A study which also focused on diagnostic confidence found that the addition of FDG-PET results to the clinical information given to 6 dementia experts increased their inter-reader reliability (kappa = 0.78) and diagnostic confidence [60].

As with amyloid, cut off levels for determining 'positivity' impact on our ability to compare datasets. A study which looked at visual versus automated analyses of both FDG and amyloid-PET [61] reported PPV, NPV and accuracy of 36.8%, 77.7% and 50% respectively, when a cut-off of 11,089 voxels was used. However, when they applied a cut-off of 8116 voxels, as used by a previous study [62], PPV and accuracy were negatively impacted (31.8% and 39.3%). This highlights the significant impact that varying cut-off levels can have on results – and questions the conclusions that can therefore be drawn.

FDG-PET has been reported by an American group to provide few benefits at a significant cost when introduced to the standard diagnostic regimes at AD centres [63]. However, the decision-analytic model used by this study looked only at those patients who had moderate to severe AD at presentation. A more recent study modelled the use of FDG-PET in relation to the validation scheme used for oncological biomarkers. They argued that thorough cost/benefit quantification is hindered by the lack of research into its estimated impact on morbidity and disability [64].

4. Conclusions

As evidenced from the literature, both amyloid and FDG-PET meet criteria for suitable biomarkers for the diagnosis of AD. [65]. They both indicate pathophysiological processes, albeit at different stages of the Alzheimer's process, and are distinct from normal patterns of aging. They have been shown to detect AD with high sensitivity and specificity compared to other neurodegenerative processes and cognitively normal age-matched individuals.

Advancements in molecular imaging serve to increase our understanding of Alzheimer's disease and its pathophysiological chronology. Interest in the role of neuroinflammation in AD has led to the development of tracers for 18 kDa translocator protein (TSPO) – a result of over-expression by activated microglia [66]. The (18)F-AV1451 tracer allows for in vivo measurement of tau and has produced results which demonstrate the relationship between the anatomical location of high tracer uptake, and the specific clinical syndrome [67]. The high specificity of tau tracers has been established by their ability to differentiate between posterior cortical atrophy (PCA) due to AD, and amnestic AD [68]. The resurgence of interest in arterial spin labelling (ASL) has sparked curiosity into the perfusion-related changes driving AD neurodegeneration [69]. Definitive models for AD remain to be defined but there is promising evidence of its ability to differentiate AD from vascular dementia.

There are, however, those who oppose the increasing use of molecular and neurodegenerative biomarkers to diagnose AD patients. Their argument is that use of these diagnostic investigations is merely academic – it will not impact on clinical management or, indeed, on patients' quality of life [70]. Nevertheless, the evidence from this review has indicated the significant proportion of cases in which use of either amyloid or FDG PET has led to an altered or earlier diagnosis. Amyloid-PET has also been approved by the European Medicines Agency for clinical trials involving the pre-dementia stage of AD [71].

As it stands currently, however, there are several cases in which amyloid and FDG-PET would not be beneficial or add to patients' management plans. *The Society of Nuclear Medicine and Molecular imaging* and the *Alzheimer's Association Amyloid Imaging Taskforce* have produced a joint set of recommendations in which PET should be performed on patients. They emphasise that, as always, clinical assessment and examination are foremost tools in a clinician's repertoire, with nuclear imaging reserved for cases of diagnostic uncertainty.

The lack of effective treatment options at present precludes the cost-effectiveness of population screening, despite high diagnostic accuracy of both biomarkers [72]. However, a 2013 study calculated that use of an imaging modality with 90% sensitivity and specificity (such as PET) in a hypothetical situation where treatment was available which halved the rate of cognitive decline, would reduce the lifetime risk of dementia of a person in their 60 s from 10.5 to 5.7% [73]. Currently, PET – particularly amyloid-PET – is an expensive imaging modality [10] that lacks sufficient standardization of its role in the AD diagnostic pathway, which in turn limits its routine application in the clinical setting. It's current importance, however, lies in its ability to sensitively and specifically select AD patients for clinical trials – the results of which would be anticipated to lead to considerable financial savings on a global healthcare scale.

Molecular imaging in AD is also hindered by the lack of a clear consensus on cut-off values for 'positive' or 'negative' amyloid and FDG-PET. While many of the studies discussed in this review detailed their own cut-off values, comparison of results between studies is impeded by use of differing values. This issue has been repeatedly highlighted by the Cochrane Group, who stressed this fact in their inability to draw meaningful conclusions from their meta-analyses on either FDG or amyloid-PET [10,74].

Future studies with standardised, uniform thresholds and a lengthier longitudinal follow-up need to be conducted to allow us to make surer conclusions about the future role of PET in clinical practice. In addition, comparison with post-mortem diagnosis, rather than clinical diagnosis with its acknowledged flaws, would result in more powerful statistical outcomes.

The true benefit of accurate and early diagnosis in AD will only be realised when successful disease modifying therapy is developed. As several potentially transformative drugs reach their phase 3 trials the importance of diagnostic accuracy in AD intensifies, and the role of both amyloid and FDG PET outside the research setting will become evident.

Conflict of interest

The authors declare no conflicts of interest

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