REVIEW ARTICLE

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The use of positron emission tomography/magnetic resonance imaging in dementia: A literature review

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Abstract

Objectives: Positron emission tomography–magnetic resonance imaging (PET/MRI) is an emerging hybrid imaging system in clinical nuclear medicine. Research demonstrates a comparative utility to current unimodal and hybrid methods, including PET-computed tomography (PET/CT), in several medical subspecialities such as neuroimaging. The aim of this review is to critically evaluate the literature from 2016 to 2021 using PET/MRI for the investigation of patients with mild cognitive impairment or dementia, and discuss the evidence base for widening its application into clinical practice.

Methods: A comprehensive literature search using the PubMed database was conducted to retrieve studies using PET/MRI in relation to the topics of mild cognitive impairment, dementia, or Alzheimer's disease between January 2016 and January 2021. This search strategy enabled studies on all dementia types to be included in the analysis. Studies were required to have a minimum of 10 human subjects and incorporate simultaneous PET/MRI.

Results: A total of 116 papers were retrieved, with 39 papers included in the final selection. These were broadly categorised into reviews (12), technical/methodological papers (11) and new data studies (16). For the current review, discussion focused on findings from the new data studies.

Conclusions: PET/MRI offers additional insight into the underlying anatomical, metabolic and functional changes associated with dementia when compared with unimodal methods and PET/CT, particularly relating to brain regions including the hippocampus and default mode network. Furthermore, the improved diagnostic utility of PET/MRI, as reported by radiologists, offers improved classification of dementia patients, with important implications for clinical management.

KEYWORDS
Alzheimer's disease, dementia, hybrid imaging, magnetic resonance imaging, mild cognitive impairment, neuroimaging, PET/MRI, positron emission tomography

Key Points

- Combined positron emission tomography–magnetic resonance imaging (PET/MRI) is an emerging imaging technique in clinical nuclear medicine.
- PET/MRI is predominantly used as a research tool in dementia.
- Improved diagnostic accuracy of PET/MRI compared to unimodal methods and PET/CT is demonstrated in other subspecialities.
- Awareness of the clinical utility of PET/MRI in dementia is growing, with earlier diagnosis having important implications for patient management.

1 | INTRODUCTION

1.1 | Background

Nuclear medicine today includes hybrid imaging modalities such as combined positron emission tomography (PET) and computed tomography (CT), improving on previously used PET-only cameras. The increased diagnostic accuracy of PET/CT, in addition to the reduction in emission scan time resulting from both lutetium-based PET scintillators, and CT-based attenuation correction[1] resulted in an economically viable product for widespread clinical use. Prior to the commercialisation of PET/CT, the concept of combining PET with magnetic resonance imaging (MRI) was already being tested,[2–4] with the first human application of PET/MRI only appearing relatively recently in the literature, initially assessing feasibility.[5,6]

Multiple considerations are needed when combining the two methods, such as the effect on electron flow in PET as a result of both static and gradient magnetic fields, as well as the disruption to the uniformity of the magnetic field resulting from PET components being placed in the MRI scanner bore.[7,8] Methods developed to overcome such technical issues are highlighted by the presence of three whole-body PET/MRI systems utilising different approaches created by GE Health Care, Philips Healthcare, and Siemens.[9]

Despite the significant economic and technical barriers, the motivation to advance the use of PET/MRI within routine clinical practice stems from the superior structural information provided by MRI compared to CT, as well as the technical advantages of improved coregistration, and service benefits associated with reducing scanning time. Using radiotracers, PET relies on the production of gamma rays from positron decay to provide functional information based on blood flow, glucose or oxygen consumption, protein synthesis, or neuroreceptor uptake.[10] Whilst PET has high specificity, anatomical information varies according to tracer used. MRI utilises a magnetic field and radiofrequency pulse to influence the axial spin of hydrogen protons, abundant in water and fat, with the energy emitted during proton relaxation used to produce highly sensitive structural images.[11] Compared to PET/CT, the soft tissue contrast, multiplanar capability, and reduced radiation dose offered by PET/MRI makes it an increasingly attractive tool, particularly within neuroimaging.

1.2 | PET/MRI in neuroimaging

Whilst used clinically in cardiology,[12] orthopaedics[13] and oncology,[14–17] the first human research PET/MRI images were of the brain.[6] PET imaging in the examination of neurotransmitter activity, neuroinflammation and haemodynamic compromise in ischaemic stroke is well-established.[18–22] Conversely, MRI is the gold standard in the assessment of brain tumours,[23] as well as in the detection of white matter (WM) damage in multiple sclerosis.[24–26] Combined, the advantages of PET/MRI in neurological investigation are increasingly documented, including the increased sensitivity of ^{18}F-fluorodeoxyglucose (FDG) PET/MRI in differentiating post-therapy tumour recurrence from fibrosis, in addition to an improved accuracy in targeting radiotherapy volumes, and overall superior image quality and artefact reduction.[27–29] Additionally, studies investigating epileptic seizure focus have shown PET/MRI to be a valid alternative to PET/CT in paediatric populations, particularly due to the reduced radiation exposure.[30]

1.3 | PET/MRI in people with dementia

Patients undergoing cognitive assessment often require routine MRI and PET imaging. MRI techniques such as diffusion tensor imaging (DTI) and functional MRI (fMRI) assist in examining functional connectivity networks implicated in dementia, such as the default mode network (DMN) composed of regions including the medial prefrontal cortex, angular gyrus and posterior cingulate cortex.[31,32] Conversely, PET has been used in differentiating clinical subtypes of dementia based on patterns of brain metabolism.[33] Recent amyloid PET radiotracers such as [^{11}C]-Pittsburgh compound-B (PIB) and fluorinated tracers which have now become licensed for clinical use provide additional information on β-amyloid plaque pathology associated with dementias such as Alzheimer's disease (AD), improving understanding of disease prevention and progression.[34] Integration of these methods to assist diagnosis and treatment of dementia is subsequently of great interest to clinicians, with the added benefit of single session multimodal image acquisition being an important consideration for patients who are often elderly or frail.[35]

1.4 | The current review

Currently, PET/MRI use in dementia is predominantly research-based, with the Dementias Platform UK establishing an innovative dementia imaging network linking PET/MRI scanners at seven UK universities, with an aim to support large scale research and clinical trials.[36] The purpose of this review is to critically examine the most recent literature published between 2016 and 2021 on the use of PET/MRI in dementia, evaluating how it compares to unimodal approaches, and discuss the evidence base for widening its application into clinical practice.

2 | METHODS

2.1 | Literature search

A literature search on the use of PET-MRI in dementia was performed in the PubMed database. The MeSH terms used to search the database were ("PET-MR" OR "PET-MRI") AND ("Dementia" OR "Mild cognitive impairment" OR "Alzheimer"). The search was undertaken on 15th January 2021 and included all papers published from 1st January 2016 until then. The search was designed to ensure that relevant papers on all dementias would be captured, as well as

papers which used the term AD (rather than Alzheimer's dementia) and studies of those with mild cognitive impairment.

2.2 | Study selection

The inclusion criteria used to screen for eligibility required papers to have been published in the last 5 years, in English, with a minimum of 10 human subjects. Additionally, only papers employing simultaneous PET/MRI imaging relating to the topic of dementia or mild cognitive impairment were selected. Papers comparing the utility of different PET radiotracers, using PET or MRI imaging separately, reports of animal studies, or papers relating to other neurological or neurodegenerative diseases were excluded from selection. Using these criteria, two researchers separately reviewed the titles and abstracts for relevance to agree a final list for inclusion.

3 | RESULTS

The results of the literature search are illustrated in Figure 1. Of the 116 studies identified using the search, 39 papers were included in the final selection, and they can be broadly categorised into 1) review
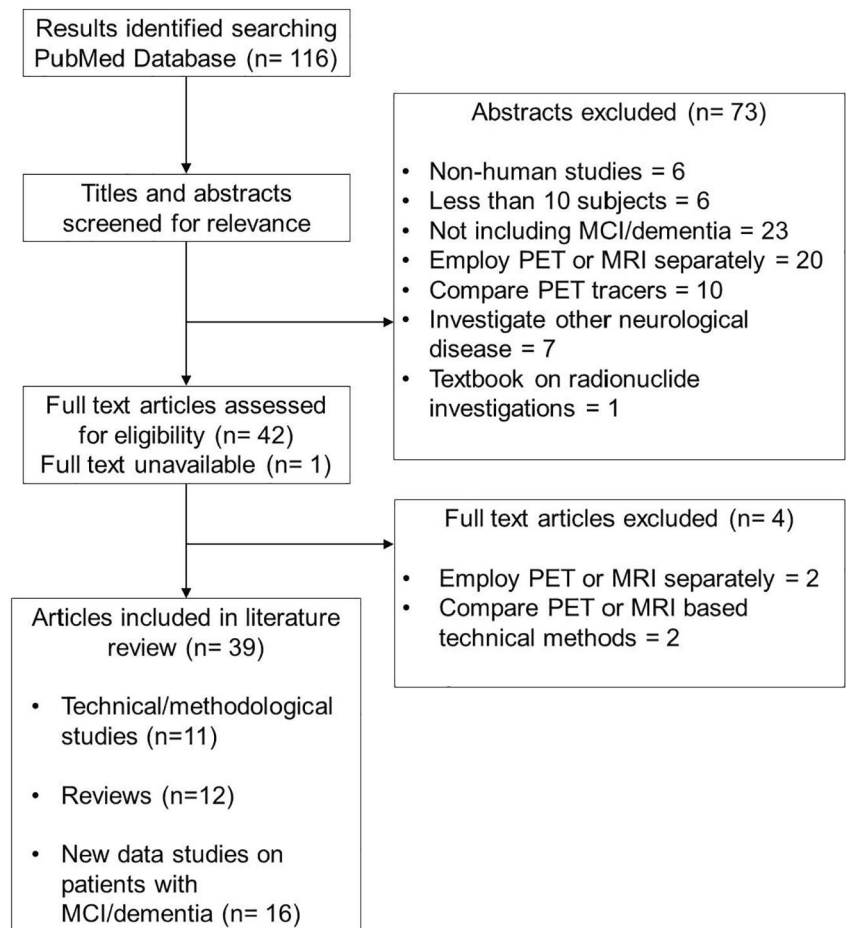

FIGURE 1 Flow chart demonstrating selection process of retrieved articles from literature search

TABLE 1 Summary of all the new data studies (*n* = 16) included in literature review

Author	Year	Journal	Aims	Patients/control subjects	PET/MRI	Main findings
[a]Franceschi et al.[37]	2021	*American Journal of Roentgenology*	Evaluate the prevalence of crossed cerebellar diaschisis (CCD) in patients undergoing ^{18}F-FDG PET/MRI for suspected neurodegenerative disease	75 patients	Integrated 3-T PET/MRI system using ^{18}F-FDG radiotracer	Results showed that 7.5% of patients had decreased FDG activity in cerebellar hemispheres contralateral to cortical hypometabolism, consistent with CDD. Six of these patients showed characteristic imaging findings of frontotemporal dementia, one had Alzheimer's dementia, and three showed corticobasal degeneration. Investigation of cerebellar metabolism could assist evaluation of patients with cognitive impairment
Tiepolt et al.[38]	2020	*European Journal of Radiology*	Examine whether Aβ-positive (AD) and Aβ-negative (non-AD) patients differ in their regional magnetic susceptibility, and if there is correlation with Aβ-load or mini mental state examination scores	11 healthy controls, 16 AD, 10 non-AD patients	Simultaneous PET/MR scanner (Biograph mMR; Siemens Healthineers) using [^{11}C]PiB	Compared with controls, AD patients showed higher QSM values in the putamen (0.049 ± 0.033 vs. 0.002 ± 0.031; $p = 0.006$). Non-AD patients showed lower QSM values in the caudate nucleus (0.003 ± 0.027 vs. 0.051 ± 0.039; $p = 0.006$). No significant correlation was found between MMSE scores and QSM values, ($p = -0.340$, $p = 0.053$, although Aβ-load and putaminal QSM values were significantly correlated ($p = -0.574$, $p = 0.020$). QSM MRI enables detection of iron pathologies associated with neurodegeneration, with implications for use as a diagnostic biomarker
Kang et al.[39]	2020	*Neuropsychiatric Disease and Treatment*	Assess the predictive ability of regional volume data provided by automated brain segmentation software for cerebral amyloid positivity in amnestic mild cognitive impairment (MCI)	58 patients with Aβ deposition and 72 without	^{11}C-PiB, 3.0T Biograph mMR (PET-MR) scanner (Siemens)	Hippocampal volume percentage of intracranial volume, normative percentiles of hippocampal volume and grey matter volume were significantly associated with Aβ positivity (all $p < 0.001$). Hippocampal volumes provided by automated segmentation software could be useful in clinical practice for screening Aβ positivity in patients with MCI
Carlson et al.[40]	2020	*Scientific Reports*	Investigate alterations in volume and metabolism using hippocampal subfield analysis and simultaneous PET/MRI on patients with MCI, AD, and healthy subjects	29 AD/MCI, 17 controls	FDG-PET scan on a 3T PET-MR (SIGNA; GE Healthcare)	MCI and AD combined group showed significantly lower left and right whole hippocampal volumes compared to controls ($p = 0.002$), more specifically subfield volumes of the dentate gyrus (DG) and cornu ammonis were significantly smaller than controls ($p = 0.003$; $p = 0.001$, respectively). FDG SUVr values for the whole hippocampus were not significantly different between MCI/AD and controls ($p = 0.166$), although a significantly lower SUVr was found in DG for combined MCI/AD compared to controls ($p = 0.009$).Subfield analysis of hippocampus demonstrates structural and metabolic changes in MCI/AD

TABLE 1 (Continued)

Author	Year	Journal	Aims	Patients/control subjects	PET/MRI	Main findings
Okazawa et al.[41]	2020	European Journal of Nuclear Medicine and Molecular Imaging	Assessing PET/MRI data simultaneously obtained from patients with early stage of Alzheimer's disease to observe changes in brain function, pathophysiology and morphology	58 patients with early dementia or MCI, 16 controls	[11C]PiB PET/MRI (Signa PET/MR; GE Healthcare)	[11C]PiB SUVr values for all regions in eAD were significantly greater than controls ($p \leq 0.00001$). Average cortical SUVr values were also signifcantly different between groups, particularly in the posterior cingulate cortex (AD vs. CTL: 2.1 ± 0.4 vs. 1.1 ± 0.2 for both sides, $p < 0.00001$). A significant correlation was found between visual scores for tracer deposition and MMSE scores ($r = 0.71$, $p < 0.0005$), but not between SUVr and MMSE ($r = 0.30$, $p > 0.05$). Regional CBF values for AD group were significantly lower in the bilateral parietal and right temporal lobes ($p < 0.05$). MRI-CBF showed greater greater regional values compared to PET-CBF, although significant differences in the posterior cingulate cortex were only demonstrated by MRI-CBF comparisons. [11C]PiB-PET/MRI provides multiple parameters to investigate pathological changes in AD
Dong et al.[42]	2020	Neurobiology of Ageing	To use DKI metrics and AWF to identify WM tracts affected by AD pathology, and to assess the relationship between Aβ deposition and WM changes in MCI/AD and healthy controls	21 mild cognitive impairment or early AD patients, 23 healthy controls	3-T integrated PET-MRI system (Siemens Biograph mMR, VB20) using 18F-Florbetapir radiotracer	Out of 44 subjects, 13 were classified as Ab−, 22 as Abi, and 9 as Ab+. No significant differences were found in WM lesion load between groups ($p = 0.84$ for Abi/Ab + comparison, $p = 0.80$ for Ab−/Abi comparison, $p = 0.56$ for Ab−/Ap−/Ap+ comparison). Tract based spatial statistics showed an overall increase in diffusion restriction from Ap− to Ai, but a decrease in diffusion restriction from Api to Ap+. Overall, found changes in opposing directionality between Ap levels and diffusion metrics, most notable in the genu of the corpus callosum and fornix. Suggests that different mechanisms affect WM microstructure during different stages of AD
Mukku et al.[43]	2019	Asian Journal of Psychiatry	Examine utility of 18F-FDG-PET/MRI brain as an investigational tool in diagnosis and subtyping of dementia	5 MCI, 16 dementia	Siemens Biograph Simultaneous PET/MRI scanner (Erlangen, Germany) with 18F-FDG radiotracer	Clinical diagnoses of MCI and dementia were established using mental state examination and associated structural MRI brain features. Based on patterns of hypometabolism, the dementia group had 7 patients with a pattern of bvFTD, 4 with AD, 1 with SD, 1 with posterior cortical atrophy, mixed AD + DLBD in 1, and no specific pattern in 2 patients. In the MCI group, patterns indicative of AD, semantic FTD, and mixed AD + FTD were found, with 2 patients showing patterns of bvFTD. 18F-FDG-PET/MRI can be used as a noninvasive emerging tool to help in dementia diagnosis and subtyping in India

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TABLE 1 (Continued)

Author	Year	Journal	Aims	Patients/control subjects	PET/MRI	Main findings
Kaltoft et al.[44]	2019	PLoS ONE	To assess the clinical value of hybrid PET/MRI in memory clinic patients, and compare the diagnostic yield of an abbreviated hybrid PET/MRI protocol with that of separate PET and standard CT	78 patients with suspected dementia	Siemens Biograph mMR 3T PET/MRI system (Siemens Healthcare)	MRI identified significantly more infarcts when compared to CT ($p < 0.001$). From 78 patients, 17% were classified partially different on PET/MRI vs. PET/CT. Additional findings on MRI included white matter lesions ($n = 3$) and atrophy ($n = 2$). There was also a significant increase in reader diagnostic confidence from PET/CT to PET/MRI ($p \leq 0.001$). Total change of interpretation of PET/MRI compared to PET/CT influenced patient diagnosis and management in 22% patients (see Appendix 1)
Riederer et al.[45]	2018	Radiology	Compare regional and quantitative measures of integrated PET/MRI hypoperfusion and hypometabolism in AD/MCI	20 patients with MCI, 11 healthy controls, 45 consecutive patients with AD	18^F-FDG PET/MRI	A reduction in CBF between patients with AD and MCI was found in multiple regions including the superior and inferior parietal cortex ($p = 0.023$, $p = 0.019$, respectively). No CBF reductions were found between the MCI and control groups. A reduction in FDG uptake and grey matter volume was found in numerous brain areas when comparing AD and MCI patients, AD and controls, and MCI and controls. Overall pulsed ASL PET/MRI showed overlapping regional and quantitative measures of hypoperfusion and hypometabolism
Marchitelli et al.[46]	2018	Neuroimage	Investigate the relationships between glucose consumption and intrinsic functional activity in healthy individuals and patients with mild AD	17 AD, 6 MCI, 23 HC	Biograph mMR MR-PET integrated system (Siemens Healthcare)	Results showed that FDG/gICA-DR correlations, used to identify common spatiotemporal patterns, allowed identification of MCI/AD patients at around 89%, with highest overlap in the DMN. In addition, FDG/ReHo, a measure of local functional connectivity, showed an 18.1% reduction in MCI/AD patients. Several clusters of brain areas showing reduced glucose consumption and functional connectivity were found, with the precuneus being consistently involved across all variables. Overall a predominant posterior cortical involvement typical of MCI/AD was found when integrating FDG-PET and fMRI
Göttler et al.[47]	2018	Journal of Cerebral Blood Flow and Metabolism	Investigate the hypothesis that impairments in vascular-haemodynamic processes underlie impairments in BOLD-FC for the pDMN in AD, independently from aberrant neuronal activity	32 patients, 22 controls	Integrated 3T Siemens mMR Biograph scanner (Siemens Healthcare)	Patients had lower BOLD-FC in the precuneus/posterior cingulate cortex and inferior parietal lobe of the DMN ($p < 0.05$). A reduction in CBF and FDG uptake was also found in the medial and lateral parietal areas of the DMN for patients. No correlation was found between CBF and FDG uptake in the DMN (patients: $r = 0.132$, $p = 0.236$; controls: $r = 0.121$, $p = 0.296$), indicating that they are separate variables. In addition, BOLD-FC was positively associated with mean CBF independently of glucose metabolism in the DMN of patients ($p = 0.050$), suggesting that an impairment in vascular haemodynamic processes contribute to impaired BOLD-FC in AD, separately to reduced neuronal activity

TABLE 1 (Continued)

Author	Year	Journal	Aims	Patients/control subjects	PET/MRI	Main findings
Schütz et al.[48]	2016	European Journal of Nuclear Medicine and Molecular Imaging	Investigate for the feasibility of combined amyloid-beta PET/MRI to provide data on amyloid beta load and medial temporal lobe atrophy, biomarkers of AD, in a single imaging session	51 patients with MCI, 28 patients with possible ADD, 16 patients with probable ADD and 5 patients with the clinical diagnosis of frontotemporal lobe degeneration (FTLD)	3-Tesla Biograph mMR (Siemens Healthcare). In 37 cases, [11C] Pittsburgh compound B ([11C]PIB) was employed as amyloid PET tracer, and in 63 cases, [18F] florbetaben	For all cases, SUVr were significantly higher in those visually assessed as amyloid beta positive compared to negative (1.61 ± 0.32 vs. 1.07 ± 0.12). 57 of the 97 subjects (59%) were evaluated as showing pathological medial temporal lobe atrophy; 26 (53%) MCI subjects, 19 (70%) patients with possible ADD, 11 (69%) patients with probable ADD, and 1 patient with FTLD. The influence of PET/MRI on the diagnosis of patients was noted in 82% of referrers. PET/MRI is a feasible method for providing information on biomarkers used in clinical diagnoses of MCI, AD and ADD
Tahmasian et al.[49]	2016	Journal of Nuclear Medicine	Examine whether multimodal neuroimaging guided by the NDH can separate individual patients with different neurodegenerative syndromes	40 patients with dementia due to different neurodegenerative syndromes (20 AD, 11 bvFTD, 4 SD, 5 PNFA	Hybrid PET/MR scanner with 18F-FDG	Results showed that classification accuracies based on DC (degree centrality), MET (glucose metabolism as) VBM (voxel-based morphometry) were 77.5% for AD, 82.5% for bvFTD, 97.5% for SD, and 87.5% for PNFA. Voxel wise multimodal classification results were also found to be superior to unimodal approaches in separating individual patients
Ding et al.[50]	2020	Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society	Explore the relevance between voxel-based glucose metabolism and functional connectivity in Chinese CD people. Explore biomarkers of CD subjects by analysing the relevance between PET and fMRI	21 healthy control subjects and 15 CD (AD + MCI)	3.0 T TOF PET/MR (SIGNA PET/MR; GE Healthcare)	Results showed SUVRs in CD group were significantly lower than HC group in the DMN (p < 0.01). Functional connectivity indexes also showed a downward trend, but no significant differences were found between the two groups. Brain regions differing in glucose metabolism and functional connectivity between CD and controls were mainly in the inferior and medial temporal lobes, angular cortex and inferior parietal lobe. DMN can be considered as an important biomarker of CD subjects in the relevance analysis between glucose metabolism and intrinsic functional connectivity
Yan et al.[51]	2020	European Journal of Nuclear Medicine and Molecular Imaging	Investigate hippocampal neurodegeneration and its associated functions in MCI and AD patients using simultaneous PET/MRI	38 MCI, 22 AD participants, 42 controls	PET/MRI (Signa PET/ MRI; GE Healthcare) using 18F-FDG radiotracer	Patient groups had significantly decreased 18F-FDG PET metabolism compared to controls, in regions including the left and right hippocampus, bilateral CA1 (cornu ammonis), bilateral CA2/3 DG (dentate gyrus), and bilateral subiculum (p ≤ 0.001). Regarding functional connectivity, AD patients showed significantly reduced connectivity compared to MCI patients in numerous hippocampal regions, with similar findings between AD patients and controls. A linear correlation was found between the left CA2/3DG volume and FDG SUVR in AD patients (p < 0.001). No other correlations were found between functional connectivity and metabolism in other hippocampal subregions (p > 0.05)

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Author	Year	Journal	Aims	Patients/control subjects	PET/MRI	Main findings
Scherr et al.[52]	2018	*Human Brain Mapping*	Applied metabolic connectivity mapping to the DMN to examine effective connectivity (EC) in patients with early AD	35 patients with early AD, including patients with mild cognitive impairment (MCI; $n = 15$) or mild dementia ($n = 20$) both due to AD, 18 matched controls	Integrated Siemens Biograph mMR scanner (Siemens)	For the combined group of patients with AD-MCI and AD-dementia, there was a significant decrease of FDG activity in all parietal regions and in the hippocampus ($p < 0.05$), but not in the prefrontal cortex ($p = 0.09$). Regarding functional connectivity, pathways between the medial prefrontal and all parietal regions were reduced in patients with early AD ($p < 0.05$). Additional reductions in connectivity were found between parietal regions in patients with AD-dementia. Reduced patterns of EC were found among DMN regions in patients with early AD, including MPFC into hippocampus ($p = 9 \times 10^{-4}$), MPFC and left parietal cortex ($p = 0.003$), and left to right parietal cortex ($p = 3 \times 10^{-4}$). Specific disruptions in EC were identified in patients with AD

Abbreviations: ^{18}F-FDG, fluorodeoxyglucose; [11C]PiB, Pittsburgh compound B; Aβ, amyloid-beta; AD, Alzheimer's disease; ADD: Alzheimer's disease dementia; ASL, arterial spin labelling; AWF, axonal water fraction; BOLD-FC, blood oxygen level dependent–functional connectivity; bvFTD, behavioural variant fronto-temporal dementia; CBF, cerebral blood flow; CD, cognitive dysfunction; DKI, diffusion kurtosis imaging; DMN, default mode network; FDG/gICA-DR, group independent component analysis and dual regression; MPFC, medial prefrontal cortex; NDH, network degeneration hypothesis; PNFA, progressive non-fluent aphasia; QSM, quantitative susceptibility mapping; ReHo, regional homogeneity; SD, semantic dementia; SUVR, standardised uptake value; WM, white matter.

[a]Full text unavailable, findings presented in abstract used for current review.

articles, 2) technical or methodological papers and 3) new data papers on patients with MCI or dementia. Full text analysis was not possible for one paper due to restricted access, with the findings presented in the abstract being used to inform the current review. A summary of the aims and main findings of the new data papers is shown in Table 1.

4 | DISCUSSION

A third of papers retrieved were review articles, highlighting an increased awareness of PET/MRI and its potential applications for dementia. Technical papers focused predominantly on attenuation correction, with results largely demonstrating the comparative efficacy of MRI-based techniques with CT-AC. Whilst these papers address important challenges faced when commercialising PET/MRI, for the purposes of this review, discussion will focus on the new data studies retrieved to assess the utility of PET/MRI as a clinical tool in dementia.

4.1 | Hippocampal studies

MRI evidence of medial temporal lobe atrophy, involving structures such as the hippocampus, entorhinal, and perirhinal cortices is well-documented in dementia.[53,54] Hippocampal regions including the cornu ammonis, and dentate gyrus are often smaller in AD/MCI patients,[55] an important biomarker for predicting AD onset.[56,57] These areas also demonstrate reduced ^{18}F-FDG-uptake in PET studies.[58] Limited studies have investigated hippocampal structural and metabolic changes using PET/MRI. Carlson et al.[40] employed ^{18}F-FDG-PET/MRI and automated hippocampal subfield-segmentation in AD/MCI patients, finding significantly lower dentate gyrus and cornu ammonis volumes, and reduced dentate gyrus FDG-SUVr compared to controls. Whole hippocampal SUVr values were not significantly different between groups. These findings support previous studies using unimodal PET and MRI, implicating the early involvement of cornu ammonis and dentate gyrus in neurodegenerative processes. However, Carlson et al. further demonstrated that at a single time-point, in the same individuals, hippocampal atrophy is more pronounced than hypometabolism, as structural differences between hippocampal regions, and between groups, were significantly more varied than SUVr values. Such findings are difficult to extrapolate from unimodal imaging studies, and may provide further insight into useful biomarkers of early disease onset. However, hippocampal volumes are shown to be influenced by early life factors, potentially affecting individual baseline values.[59] Additionally, AD/MCI patients were grouped together to increase statistical power, which may influence the applicability of these findings to patients at varying disease stages. Despite this, the authors noted an improved spatial alignment between PET and MRI images due to intrinsic scanner coregistration, reducing issues such as misalignment and spatial intensity distortion associated with coregistering unimodal images.[60]

Kang et al.[39] similarly used automated brain segmentation software and [^{11}C]PiB PET/MRI to demonstrate the predictive ability of hippocampal regional volume on the presence of Aβ, an important predictor of dementia development.[61] These findings support the association between early memory deficits and hippocampal atrophy,[55] and further demonstrate the relationship between these structural changes and developing Aβ pathology in MCI. Although MRI is widely used to assess structural abnormalities associated with neurodegeneration,[55] the additional screening for Aβ load using [^{11}C] PiB has important clinical implications for PET/MRI, as earlier detection of such biomarkers improves opportunities for active intervention. However, this study also assessed the utility of a newly approved segmentation software, with more studies applying this specific package to PET/MRI needed to substantiate their findings. Additionally, risk factors such as cardiovascular disease, which have the potential to confound brain volume assessment, were not accounted for in patient selection or statistical analyses. Despite these limitations, Kang et al. demonstrate the utility of PET/MRI in predicting early Aβ pathology using multimodal parameters in a single imaging session.

A further study by Yan et al.[51] used PET/fMRI to investigate the relationship between hippocampal structure and metabolism, and resulting effects on functional connectivity in AD/MCI patients. Results showed a significant reduction in both ^{18}F-FDG-SUVr and functional connectivity in most hippocampal subregions in AD patients, and significantly reduced connectivity between the hippocampus and frontal regions including the superior medial frontal gyrus and precuneus, supporting previous fMRI and PET studies.[62] Researchers also reported a significant negative correlation between ^{18}F-FDG hypometabolism and decreased left cornu ammonis/dentate gyrus-superior medial frontal gyrus connectivity in AD patients, a finding corresponding to previous fMRI studies showing that increased activity in cornu ammonis/dentate gyrus is associated with reduced cognitive function,[63] and can be therapeutically targeted.[64] The relationship between hippocampal functional connectivity and metabolism demonstrated by PET/fMRI in this study improves on previous findings using unimodal techniques, and allows for a more comprehensive understanding of underlying neurodegenerative processes occurring at the subregional hippocampal level.

4.2 | Functional connectivity studies

The default mode network is a tightly connected functional brain network important in memory function, studied previously using predominantly fMRI.[31,32] Employing ^{18}F-FDG-PET/fMRI, Marchitelli et al.[46] investigated the relationship between glucose metabolism and neuronal activity in patients with AD/MCI, and examined within-subject correlations between ^{18}FDG-PET and fMRI metrics measuring local connectivity and spatiotemporal patterns. Both ^{18}FDG-PET and fMRI metrics independently differentiated AD/MCI patients from healthy controls, with posterior DMN regions exhibiting the greatest changes. Similar findings using PET/MRI are

reported by both Ding et al.[50] and Scherr et al.[52] Moreover, within-subject PET/fMRI correlations showed a 17% reduction in AD/MCI patients compared to controls. These findings support prior unimodal studies[65–67] and go further to provide evidence for the theory that glucose-mediated CBF regulation and glucose/oxygen coupling deteriorates with AD disease progression.[68]

Limitations of this study include the finding that DMN hypometabolism in AD/MCI patients was more extensive than patterns of hypoconnectivity. [18]FDG metabolism reflects resting-state glucose mobilisation and is largely unaffected by physiological artefacts,[69] whereas the blood-oxygen level-dependent (BOLD) signal is a haemodynamic measure of oxygen consumption, and can be influenced by altered physiological conditions.[70] These differences could therefore bias the combined used of PET/fMRI metrics when interpreting underlying DMN changes in AD/MCI. However, Göttler et al.[47] found that whilst overlapping changes in BOLD signal, [18]FDG uptake, and CBF were found in the DMN of AD patients, reductions in BOLD signal were correlated with reduced CBF independently from [18]FDG-PET hypometabolism. This suggests that altered BOLD signals found in AD/MCI patients can reflect impairments in haemodynamic processes separately from changes in neuronal activity. Regional reductions in CBF for AD patients was also found by Okazawa[41] and Riederer.[45] Altogether, the use of both fMRI BOLD signal and [18]FDG-PET data in these studies allows for a unique insight into simultaneous neurodegenerative processes underlying AD in a way that cannot be achieved using unimodal imaging methods.

PET/MRI has also been used to investigate WM tracts forming the basis of functional brain networks such as the DMN, as WM damage is consistently observed in AD postmortem studies.[71] There is also increasing evidence that neurodegeneration spreads via brain networks.[72] DTI, an MRI method based on the measurement of water molecule diffusion in different tissues, has demonstrated WM changes in AD patients.[73] Dong et al.[42] used amyloid tracer ^{18}F-Florbetapir and PET/DTI-MRI to examine the relationship between WM changes and Aβ deposition in AD/MCI patients, demonstrating WM changes in tracts such as the anterior corona radiata and genu of the corpus callosum. The benefits of integrating MRI techniques with PET amyloid tracers is further highlighted by Tiepolt[38] who combined [^{11}C]PiB-PET with quantitative susceptibility mapping, an MRI technique measuring the magnetic susceptibility of brain regions as a consequence of iron deposition. Findings suggested a relationship between Aβ load and putaminal iron deposition in AD patients. Although this requires further investigation, additional discoveries of such biomarkers is possible if PET/MRI were more widely available.

Moving beyond the cerebrum, Franceschi et al.[37] used [18]FDG-PET/MRI to examine neurodegeneration within the corticopontine-cerebellar pathway. Results showed decreased [18]FDG activity in the contralateral cerebellar hemisphere to supratentorial hypometabolism, providing support for the presence of crossed cerebellar diaschisis in dementia, a common finding in neurological disease, and further demonstrated this to be more common in FTD compared to other dementias. Although further research is needed to clarify the relationship between PET and MRI metrics when examining

functional connectivity in dementia, the overall benefit shown by these studies of simultaneous image acquisition at a single point in time and physiological state is important for advancing understanding of disease stage and pathology, with subsequent implications for earlier clinical intervention.

4.3 | Diagnostic utility

An important consideration for the clinical applicability of PET/MRI in dementia is the perception of clinical utility. Compared to other cerebral disorders (e.g., tumours, stroke), dementia and associated pathology is underemphasised in radiology teaching, with few radiological reports suggesting dementia diagnoses despite identification of characteristic atrophy patterns.[74] In practice, MRI and PET images are often interpreted by different subspecialist radiologists, with integration of these separate findings often left to the referring clinician.[75] Mukku et al.[43] examined the diagnostic utility of [18]FDG-PET/MRI in dementia diagnoses, finding that biomarkers of hypometabolism and structural atrophy showed 90.5% concordance with clinical diagnoses, and further assisted with diagnostic subtyping. Although offering limited benefit in two patients, the authors note that PET/MRI reduced the need for sedation in distressed cognitively-impaired patients due to its relative simplicity and reduced scanning time. Tahmasian et al.[49] reported a similar benefit of multimodal imaging for differentiating dementia subtypes. Using [18]FDG-PET/MRI, they found classification accuracies to be between 77.5% and 97.5% for subtypes including bvFTD, SD, and PNFA, findings that were significantly superior to unimodal approaches.

Further support is provided by Schutz et al.[48] who employed both [^{11}C]PIB and ^{18}F-florbetaben amyloid PET tracers, finding that PET/MRI assisted diagnostic categorisation in 67% of patients independent of MTL atrophy and amyloid load biomarkers. Furthermore, 82% of referrers noted the significant influence PET/MRI had on final diagnoses. This positive reception was also reported by Kaltoft et al.[44] who found that radiologist confidence ratings for the diagnostic classification of memory clinic patients were significantly greater for PET/MRI images compared to PET/CT. Additionally, PET/MRI identified significantly more vascular pathologies, which altered diagnoses in 17% of patients. Furthermore, reclassification of patients using PET/MRI had a major clinical impact on management in 22% of patients. This is the only study directly comparing the two hybrid techniques within this review, a comparison that is desperately needed to better assess the extent to which PET/MRI can aid clinical practice.

5 | CONCLUSION

This review examined studies published in the last 5 years on the use of PET/MRI in dementia in order to identify the advantages and possible disadvantages of this hybrid method for clinical application. Overall, new data studies investigating the role of the hippocampus

and DMN in neurodegenerative disease demonstrate the added insight provided by PET/MRI into underlying anatomical, metabolic, and functional changes associated with disease progression, and importantly, how such processes are interlinked. Further to this, research accounting for the perceived diagnostic utility and overall approachability of PET/MRI for radiologists demonstrates its capability of matching, and arguably surpassing current methods used in dementia care, although further studies providing direct comparisons with PET/CT are critical. In conclusion, whilst PET/MRI currently exists as a predominantly research-based tool in dementia, the current review demonstrates that not only does PET/MRI offer comparative feasibility to unimodal methods and PET/CT, it could improve diagnostic classification of dementia patients, with important implications for clinical management.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

John T. O'Brien conceived the review. Nicole Lorking produced the written draft with tables and figures. Both John T. O'Brien and Alison D. Murray contributed to revisions and gave final approval of the version to be published.

DATA AVAILABILITY STATEMENT

Data is available on reasonable request from the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.