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Amyloid imaging in dementia

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Summary

A major advancement in the field of medicine has been the timely advent of amyloid imaging, which has allowed critical evaluation of the complex relationship between amyloid β peptide (Aβ) aggregation and Alzheimer's disease *in vivo*. Most importantly, amyloid imaging has the potential to detect Aβ in mildly affected as well as asymptomatic individuals, when the therapeutic window of opportunity might still be open to pharmacological intervention. It also shows significant promise in differential diagnosis of mild cognitive impairment or atypical dementias. Amyloid imaging studies support a model in which amyloid aggregation is considered an early event on the path of dementia, beginning insidiously in cognitively healthy individuals being accompanied by subtle cognitive, functional and structural brain alterations suggestive of incipient AD. As individuals progress to dementia, clinical decline and neurodegeneration accelerate and might proceed independently of amyloid accumulation. In this review we focus on amyloid imaging with particular emphasis on [^{11}C]PIB in AD, mild cognitive impairment and other dementias, and discuss the advances made in this perplexing field.

Key words: amyloid imaging, [^{11}C]PIB-PET, Alzheimer's disease, mild cognitive impairment, cognitively normal controls.

Introduction

Dementia is a progressive neurodegenerative disease, and is set to become the developed world's largest socio-economic healthcare burden over coming decades. According to different estimates, between 2 and 10% of all cases of dementia start before the age of 65 and the prevalence doubles with every 5-year increment in age after 65. The number of people globally who are living with dementia is estimated to be 35.6 million, and epidemiological studies indicate that this number is expected to grow at an alarming rate. It is estimated that numbers will nearly double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050 (Alzheimer's Disease International, World Alzheimer Report 2010). Currently, in the UK, there are 800,000 people living with dementia and over 17,000 younger people (65 years of age or below) have dementia. As the size of the population is growing and people are living longer, by 2021 there will be over 1 million people living with dementia in the UK. This is costing the NHS, local authorities and families £23 billion a year and this will grow to £27 billion by 2018 (Dementia 2012: A national challenge).

The term 'dementia' is used to describe a syndrome that may be caused by a number of illnesses in which there is progressive decline in multiple areas of function, including decline in memory, reasoning, communication skills and the ability to carry out activities of daily living. Alongside this decline, individuals may develop behavioural and psychological symptoms such as depression, psychosis, aggression and wandering, which cause problems in themselves, which complicate care, and which can occur at any stage of the illness. Alzheimer's disease is the most common form of dementia, accounting for 62% of dementia cases. Other forms of dementia include vascular dementia (17%), mixed (AD and vascular) dementia (10%), dementia with Lewy bodies (4%), fronto-temporal dementia (2%) and Parkinson's dementia (2%) (Dementia 2012: A national challenge).

AD is a complex neurodegenerative disorder of which the exact cause is still unclear. There are currently no effective disease-modifying therapies and the only available treatments are symptomatic. The incurable nature of AD presents a great challenge for healthcare systems and considerable resources have focused on developing therapeutic agents to directly delay the pathophysiological processes. As we persist in the search for a cure, there has been significant progress in the understanding of the pathophysiological events that cause the disease with a focus on

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amyloid formation. The underlying pathology of Alzheimer's disease is believed to precede the onset of clinical symptoms by many years.[1] The clinical diagnosis of AD is defined by NINDS-ADRDA[2] and DSM-IV criteria. However, these criteria have been revised to include the biomarkers, and revised criteria have been developed by the joint National Institute of Ageing and Alzheimer's Association (NIA-AA criteria) for the purpose of research.[3]

Mild cognitive impairment (MCI) refers to a transitional state between the cognition of normal ageing and mild dementia. Amnestic mild cognitive impairment (aMCI) refers to individuals who have isolated impairment of short-term recall but otherwise intact higher function and do not meet DSM-IV criteria for dementia. The initial criteria were set out by Petersen *et al*.,[4] and include: (1) memory complaint, preferably corroborated by an informant; (2) impaired memory function for age and education; (3) preserved general cognitive function; and (4) intact activities of daily living. Patients with aMCI are at a higher risk of developing Alzheimer's disease, and 10–15% convert to AD per year, compared with healthy control subjects who convert at a rate of 1–2% per year.[4–6] NIA-AA criteria divide MCI into early and late MCI depending on the appearance of imaging and CSF biomarkers.

Amyloid cascade hypothesis

The most widely accepted hypothesis to describe the aetiology of AD remains the amyloid cascade hypothesis. Within this hypothesis it is assumed that the amyloid β peptide (Aβ) is the prime initiator of AD pathology, where altered amyloid precursor protein (APP) processing leads to generation of toxic Aβ species. Aβ is considered as the primary influence that triggers significant biochemical and histological alterations driving tau hyperphosphorylation and other downstream events including inflammation, ultimately resulting in neuronal dysfunction and death. These changes manifest clinically in the form of dementia, which is irreversibly progressive.[7] In line with the amyloid cascade hypothesis, anti-amyloid therapies have been tried in AD, without great success. This could be because amyloid deposition putatively causes severe damage to neurons many years ahead of the clinical onset of dementia, hence a therapeutic window of opportunity may have already been lost, where the neuronal damage has already set in. Hence anti-amyloid therapies are now focusing on MCI stage. Interestingly, pathological studies have demonstrated that amyloid deposition can also occur in normal, healthy ageing. However, pathological studies that are almost always cross-sectional suffer from a limitation in that no longitudinal outcome data are attainable. This implies that it is virtually impossible to determine the sequence of events occurring early on in the disease process, and one cannot study the temporal relationship between key events. In quest of the pathophysiological conspirators in the disease process, the onus has now shifted towards identifying the disease early on in its pathogenesis, and to accurately monitor its progression. A major advancement in this arcane field of medicine has been the timely advent of amyloid imaging, which allows us to critically evaluate the complex relationship between Aβ aggregation and AD *in vivo*. Most importantly, amyloid imaging has the potential to detect Aβ in mildly affected as well as asymptomatic individuals, when the therapeutic window of opportunity might still be open to pharmacological intervention. In this review we focus on amyloid imaging in different diseases and the advances made in this field.

Search strategy and selection criteria

PubMed was searched for papers that were published before June 2012. The following key words were used in the search: 'positron emission tomography', 'amyloid imaging', '[^{11}C]PIB', 'dementia', 'Alzheimer's disease', 'mild cognitive impairment', 'Lewy body disease', 'frontotemporal dementia' and 'non-demented'. The selected articles were examined for additional references not revealed by automated searches. Only articles published in English were considered.

Amyloid imaging

Amyloid imaging is the principal method for the detection of Aβ pathology; however, it is well known that no *in vivo* assessment of pathology is as sensitive as post-mortem histological and biochemical assessment.[8] During the past 8 years amyloid imaging has established itself alongside magnetic resonance imaging (MRI) and fluorodeoxyglucose positron emission tomography

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Table 1. *Amyloid PET tracers*

Parent compound	Tracer
Thioflavin	[^{11}C]PIB – Pittsburgh compound-B (2-[4¢-(methylamino)phenyl]-6-hydroxybenzothiazole)
Benzofuran	[^{11}C]AZD2184 (N-[^{11}C]methyl)-2-(6-methylamino-pyridin-3-yl)-benzo[d]thiazol-6-ol)
Benzoxazole	[^{11}C]-BF-227 ([^{11}C]2-(2-[2 dimethylaminothiazol-5-yl]ethenyl)-6-(2 [fluoro]ethoxy)benzoxazole)
Stilbene	[^{11}C]SB13 – 4-*N*-methylamino-4¢ hydroxystilbene
Naphthol	[^{18}F]FDDNP (2-(1–6-[(2 fluoroethyl(methyl)amino]-2-naphthylethylidene)malononitrile)
Thioflavin	[^{18}F]Flutemetamol/GE-067 (2-[3-[^{18}F]fluoro-4 (methylamino)phenyl]1,3-benzothiazol-6-ol)
Stilbene	^{18}F-AV1/BAY94–9172 – 4-(*N*-methylamino)-4¢-(2-(2-(2 fluoroethoxy)ethoxy)ethoxy)stilbene
Styrylpyridine	[^{18}F]Florbetapir ([^{18}F]AV-45, (E)-2-(2-(2-(2-[^{18}F]fluoroethoxy)ethoxy)ethoxy,)-5-(4-methylaminostyryl)pyridine, Amyvid
Benzofuran	[^{18}F]AZD4694 (2-(2-fluoro-6-methylamino-pyridin-3-yl)-benzofuran-5-ol)

(FDG-PET) as an important neuroimaging tool for the investigation of brain ageing and dementia.[9]

Amyloid imaging agents will detect beta-sheet rich fibrillar deposits of Aβ protein in plaques in AD and cerebrovascular amyloid (CAA).[8] Positron emission tomography (PET) is a well-established imaging modality. PET employs biologically active molecules in micromolar or nanomolar concentrations that have been labelled with short-lived positron-emitting isotopes such as ^{15}O (half-life 2 min), ^{11}C (20 min) and ^{18}F (110 min). The very short half-lives of O-15 and C-11 restrict their use to fully equipped PET centres with a cyclotron and radiopharmaceutical laboratory. F-18-labelled tracers can be produced in specialized centres and distributed regionally to hospitals running a PET scanner only. The physical characteristics of these isotopes and the molecular specificity of labelled molecules, combined with the high detection efficacy of modern PET scanners, provide sensitivity for human *in vivo* measurement of indicator concentrations that is several orders of magnitude higher than with the other imaging techniques.[9]

Tracers that have so far progressed into humans include [^{18}F]FDDNP,[10] [^{11}C]PIB,[11] [^{11}C]AZD2184,[12] [^{11}C]BF-227,[13] [^{11}C]SB13,[14] [^{18}F]Flutemetamol,[15] [^{18}F]AV1 ([^{18}F]Florbetaben),[16] [^{18}F]Florbetapir[17] and [^{18}F]AZD4694[18,19] (Table 1). Of these tracers, only PIB has received an extensive biochemical profiling of its binding to a range of *in vitro* amyloid filaments[20–22] and neuropathological lesions.[22,23]

PIB

Currently the most widely studied PET tracer and an analogue of the amyloid-binding dye thioflavin-T is Pittsburgh Compound B (PIB). Modification of the polar amyloid binding histological dye, thioflavin-T, led to the finding that neutral benzothiazoles also bind to amyloid with high affinity and additionally cross the blood–brain barrier. It is shown benzothiazole amyloid binding agent 2-(4'-methyl amino phenyl) benzothiazole (called BTA-1) and related compounds bind to amyloid with low nanomolar affinity, enter the brain at levels sufficient for yielding a PET signal and clear rapidly from normal brain tissue. At the low nanomolar concentrations typically administered during PET studies, BTA-1 binds to extracellular amyloid plaques in post-mortem brain slices but not to intracellular neurofibrillary tangles or Lewy bodies. *In vitro* studies suggest that, while BTA-1 binds to fibrillar Aβ deposits found in the cortex and striatum, it does not bind to amorphous Aβ deposits such as those found in cerebellum.[20] The first direct *in vivo* visualization of brain amyloid was carried out in mild AD patients, where uptake patterns were in keeping with amyloid plaque deposition described in post-mortem studies of AD brains.[11] [^{11}C]PIB binds to fibrillar amyloid with no detectable binding to soluble Aβ forms or neurofibrillary tangles at PET tracer concentrations.[24]

The aim of the present review is to discuss the current state of amyloid imaging, focusing on [^{11}C]PIB in AD, MCI and healthy control subjects.

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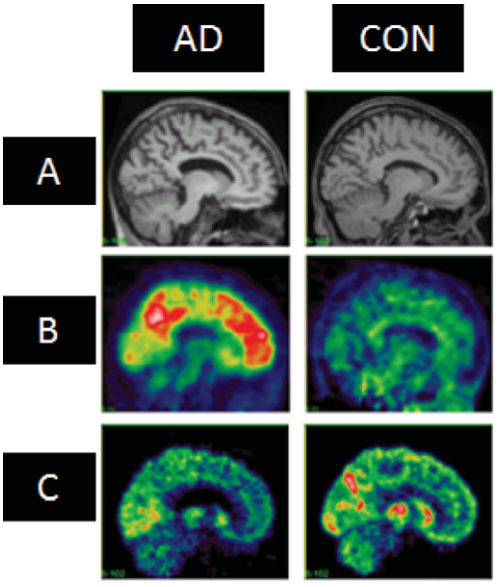


Figure 1. Representative images from Alzheimer's disease (AD) subjects and healthy control (CON) subjects showing median sagittal MRI (A) and PET with [^{11}C]PIB (B) and [^{18}F]FDG (C). Increased [^{11}C]PIB retention is observed in AD subjects, with the highest tracer retention observed in frontal, temporal and posterior cingulate cortices compared with healthy control subjects (B). Glucose hypometabolism is most consistently observed in the temporoparietal regions in AD subjects compared with healthy controls (C).

Amyloid imaging in Alzheimer's disease

Within the past decade, several [^{11}C]PIB-PET studies performed on AD subjects have demonstrated 2-fold increases or more in [^{11}C]PIB retention in predominantly cortical areas compared with healthy control subjects (Figure 1), as judged either by visual assessment or quantitative analysis of tracer uptake.[11,25–27] More specifically, using the region of interest and/or voxel-wise analysis, the highest tracer uptake is consistently observed in prefrontal cortex, precuneus and posterior cingulate cortex, followed intimately by lateral parietal and temporal cortex along with striatum in AD subjects compared with healthy controls.[11,25–28] This is in keeping with the neuropathological observations of Aβ fibrillar plaques.[1,29] A relatively lower tracer uptake is found in the occipital cortex, globus pallidus and thalamus, whilst primary sensorimotor and visual cortices in addition to medial temporal lobe regions are relatively spared.[30] Cerebellar grey matter exhibits very little if any [^{11}C]PIB binding, allowing the cerebellum to be used frequently as a reliable reference region. Although graphical Logan analysis which uses arterial plasma input function has been suggested to be the gold standard for [^{11}C]PIB-PET analysis, the use of target to cerebellum uptake ratios generates comparable results to Logan plot derived distribution volume ratios.[31,32] It is a very effective method, which is simpler to generate and shortens the scan time considerably. Interestingly, pathological studies examining cases with Prion disease have demonstrated significant amyloid deposits in the cerebellum.[33,34] Moreover, a recent [^{11}C]PIB study reported significant amyloid deposition in the cerebellum of familial AD subjects.[35] The cerebellum especially in these cases, is not always a suitable non-specific reference for quantification of [^{11}C]PIB-PET, hence the pons should be considered.[36,37]

Several longitudinal studies using [^{11}C]PIB have been conducted to monitor the disease progression in AD. Engler *et al.* re-scanned 16 patients with mild AD who were included in their original study after 2.0 $\pm$ 0.5 years.[38] [^{11}C]PIB retention remained stable between the baseline and the 2-year follow-up period, suggesting the notion that amyloid deposition reaches a plateau by the early clinical stages of the disease, in line with the amyloid cascade hypothesis. There was a clear dissociation between the amyloid load, which remained relatively stable with minor variations, and clinical status, which continued to decline in a number of subjects. Furthermore, the cognitive decline was more accurately associated and correlated with the progressive deterioration in glucose metabolism measured by [^{18}F]FDG.[38] Jack and colleagues reported similar results when examining alterations in [^{11}C]PIB uptake and brain atrophy over a year in a study comprising 21 healthy controls, 32 MCI and 8 AD subjects. They found small, insignificant increases in [^{11}C]PIB retention in AD; however, this value was identical to the other diagnostic groups across the same brain regions. In contrast, the rates of brain atrophy as measured by changes in ventricular volume differed significantly between the groups and perhaps not surprisingly were highest in AD followed sequentially by MCI and controls. Moreover, the clinical decline revealed by longitudinal analysis strongly correlated with

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brain atrophy rates but not with changes in global [^{11}C]PIB, and no association between brain atrophy and global [^{11}C]PIB rates was detected.[39] The above observations are in agreement with other follow-up [^{11}C]PIB studies, which found no elevations in [^{11}C]PIB uptake after 2 years[40] and 5 years.[41] In accordance with previous studies,[38] Kadir *et al*.[41] found considerable variability between subjects, with some demonstrating small increases in [^{11}C]PIB and others exhibiting reduced [^{11}C]PIB uptake. The latter finding is interesting and warrants further mention. Although the exact proportionality of fibrillar and oligomeric species of Aβ in AD remains ambiguous, the existence of a continuous dynamic equilibrium between amyloid plaques and oligomers cannot be ruled out.[42] Since an exchange between fibrillar and oligomeric Aβ surrounding plaques has been reported in transgenic APP mice,[43] this suggests that a similar mechanism might be operant in AD and might be the reason for the observed decrease in levels of fibrillar Aβ forms.[44] More interestingly, recent data do indicate that benign insoluble aggregates may slowly leach to form toxic oligomers.[45] One of the caveats of the Kadir *et al*. study is that no correction for partial volume effects was performed and it cannot be ruled out that a proportion of the lower PIB binding observed may be due to the atrophy in later stages of the disease.[41]

Amyloid imaging in mild cognitive impairment

It is believed that amyloid deposition occurs decades before any cognitive changes at a clinical level are established and begins to accelerate in the pre-clinical stage of AD, before reaching a relative plateau at the onset of symptoms. Presumably, MCI individuals with underlying AD pathology are at an increased risk of progressing to dementia. Amyloid imaging can potentially identify early AD pathology in MCI and can help predict the rate of progression from MCI to dementia of AD type or other dementias.

Several studies in MCI have demonstrated that [^{11}C]PIB uptake is intermediate between AD and controls.[27,46–48] In the majority of studies, [^{11}C]PIB binding in MCI subjects is bi-modally distributed, with one subset of subjects demonstrating AD-like uptake levels, and the other showing low, control-like [^{11}C]PIB values.[25,27,31,47–51] Depending on the criteria used to diagnose MCI and the threshold used to define [^{11}C]PIB positivity, around 52–87% of MCI subjects demonstrate elevated [^{11}C]PIB binding.[25,27,31,47–51] It has been established that individuals meeting the criteria for amnestic MCI are more likely to be [^{11}C]PIB positive than patients diagnosed with non-amnestic MCI.[50,51] Moreover, ApoE4 carriers have a greater propensity to accumulate amyloid deposits and hence are more likely to show [^{11}C]PIB positivity compared with non-ApoE4 carriers.[51,52] Interestingly, cross-sectional analysis of [^{11}C]PIB-positive compared with [^{11}C]PIB-negative MCI subjects reveal lower performance on episodic memory tasks in a few studies[51] but not others.[25,27]

To date, a consensus regarding the cut-off values used to determine [^{11}C]PIB positivity or negativity has not been reached due to paucity of available data on older cognitively normal individuals. This is because classification of subjects as either being [^{11}C]PIB-positive or -negative relies on the distribution of [^{11}C]PIB values present in the healthy control group under investigation. This may be the reason for the generation of different cut-off values and the lack of consensus reported amongst groups. Some groups treat amyloid deposition as a continuous variable,[48,51] whereas other groups have dichotomized subjects into [^{11}C]PIB-positive or -negative groups albeit with variability in their categorzation approaches.[25,27,53] Although different research groups have different [^{11}C]PIB cut-off values, most are within a few percentage points of each other. Recent analysis in conjunction with pathological studies suggest a biological relevance of slight [^{11}C]PIB accumulations in ageing.[54]

Longitudinal studies investigating [^{11}C]PIB uptake in MCI subjects have yielded mixed results. A recent 2-year longitudinal study involving 29 amnestic MCI subjects did not demonstrate any significant elevations in [^{11}C]PIB uptake despite significant progression in hippocampal atrophy in the 17/29 (59%) subjects who progressed to develop AD,[55] consistent with other studies.[56] Based on these observations, it may be suggested that amyloid deposition approaches a plateau by early stages of AD despite an ongoing decline in cognition. Contrary to this, Villemagne and colleagues have reported significant increases in overall amyloid burden in AD and MCI subjects at 2-year follow-up. AD subjects showed increases in [^{11}C]PIB uptake of 91% over 20 months ranging

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from 1 to 18% with greater [^{11}C]PIB retention in mild AD than more severe dementia. Meanwhile, the MCI group demonstrated an overall, significant increase of 2.1% ($P < 0.02$) in [^{11}C]PIB uptake over a period of 20 months. Additionally, 12/65 MCI patients were followed up for 3 years and they demonstrated an increase of 5.5% in amyloid load.[57] Jack *et al*.[39] reported an annual increase of 1.7% in 32 MCI subjects studied, and emerging studies[58] continue to challenge the theory that amyloid plaque load reaches a plateau in the prodromal stage of AD. The amyloid deposition begins in the pre-dementia phase but continues in subjects with mild to moderate AD and only halts in the latter stages of the disease.[57]

Early detection of AD pathology by way of amyloid imaging is of paramount importance as it could help identify MCI subjects who are more likely to progress over a specified time to AD. Forsberg *et al*. showed that 33% (7/21) of MCI subjects with increased [^{11}C]PIB uptake converted to AD after a mean of 8.1 ± 6.0 months of clinical follow-up, whilst individuals with normal [^{11}C]PIB uptake at baseline retained a diagnosis of MCI.[50] Similarly, a study showed that 38% (5/13) of the [^{11}C]PIB-positive MCI subjects later converted to AD.[59] Okello *et al*.[46] analysed [^{11}C]PIB scans of 31 amnestic MCI subjects over a period of 3 years and found that 14 out of the 17 (82%) [^{11}C]PIB-positive subjects progressed to AD whilst only one of the 14 [^{11}C]PIB-negative subjects converted to AD. Furthermore, the fastest converters demonstrated the highest [^{11}C]PIB baseline uptake in the anterior cingulate and frontal cortex.[52] In a seminal study, it was found that 67% of the [^{11}C]PIB-positive MCI subjects converted to AD over 2 years compared with only 5% of [^{11}C]PIB-negative MCI subjects.[57] Interestingly, of the five [^{11}C]PIB-negative MCI subjects, only one developed AD, whilst the rest converted to other types of dementia including vascular dementia (one subject), frontotemporal lobar degeneration (FTLD, one subject) and dementia with Lewy bodies (two subjects). Villemagne *et al*. suggested that MCI subjects with increased Aβ deposition are 13 times more likely to develop AD compared with those with low Aβ deposition.[57] More importantly, the fact that a few [^{11}C]PIB-negative subjects can also progress to AD may suggest that amyloid plaques may not directly be responsible for the neuronal dysfunction of this disorder. An alternative explanation is that oligomeric Aβ species or non-fibrillar diffuse plaques that evade detection by [^{11}C]PIB might be predominant in the [^{11}C]PIB-negative MCI subjects, who might be in their earlier stages of the disease. Another plausible explanation is that the cause of the impairment may be due to a non-AD process, such as cerebrovascular pathology, tauopathy, etc. In summary, an elevated [^{11}C]PIB retention implies that the baseline appears to be highly suggestive of future progression from MCI to AD. On the other hand, the few MCI subjects with negative [^{11}C]PIB scans tend to progress to dementia of non-AD types.

Amyloid imaging in cognitively normal controls

Neuropathological studies carried out on post-mortem brain tissues have reported an increased prevalence of AD pathology in elderly non-demented individuals. For instance, post-mortem data has demonstrated that around 25–45% of the otherwise cognitively normal individuals above the age of 75 exhibit pathological changes indistinguishable from that observed in AD.[60] Consistent with this, depending on the age of the cohort and the threshold used to define [^{11}C]PIB positivity, elevated [^{11}C]PIB binding has been reported in 10–30% of the healthy control cases.[11,25,48,51,53,57,61–64] On the contrary, no elevation in [^{11}C]PIB binding has been reported in young normal controls.[11,64] [^{11}C]PIB uptake in older controls falls along a continuum between the low binding observed in young controls and the high levels observed in AD. In [^{11}C]PIB-positive subjects, the distribution of uptake is similar to AD and involves neocortical regions including prefrontal cortex, parietal regions, lateral temporal cortex and striatum.[65,66] However, focal binding in control subjects has been observed in occipital cortex but this pattern is suggestive of vascular amyloid deposition.[61]

PET provides an excellent opportunity to analyse the regional distribution of amyloid plaques *in vivo* as a means to predict subjects who are at risk of acquiring AD through longitudinal observations. In addition, amyloid imaging allows for more rigorous quantification of distribution and burden of amyloid, and permits direct comparison of these measures to simultaneously derived cognitive metrics. This is in contrast to the post-mortem studies where significant

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delay between behavioural and histopathological assessment is observed.[30]

To the best of our knowledge, the largest study to date has utilized 408 cognitively normal non-demented older subjects to study the association between Aβ load and cognitive function and the effect of ApoE4 status on the aforementioned association.[67] According to the appropriate cut-off values used to describe [^{11}C]PIB positivity, 34% of the healthy subjects showed elevated uptake. In this seminal study, greater [^{11}C]PIB uptake was associated with worse cognitive function and the decline in cognition appeared to be the steepest in ApoE4 carriers.[67] ApoE4 is considered to be the most important genetic risk factor for AD as consistently confirmed by a wide range of [^{11}C]PIB-PET studies[64,68] as well as genome wide association studies.[69] It may increase the risk of getting the disease partly by influencing Aβ clearance and fibrillogenesis. Furthermore, longitudinal studies have demonstrated that ApoE4 carriers have a faster rate of progression from MCI to AD[55] and that MCI converters compared with non-MCI converters have a higher prevalence of ApoE4 allele.[52]

A retrospective study carried out by Villemagne *et al*. in which they examined cognitive test scores over 6–10 years in 34 subjects, who underwent [^{11}C]PIB-PET scans, showed that [^{11}C]PIB positivity was found in 70% of subjects with declining cognitive scores compared with the 17% of those with stable scores.[63] A recent longitudinal study by the same group demonstrated [^{11}C]PIB positivity in 33 of the 106 (31%) cognitively healthy participants. During a follow-up period of 3 years, eight of the subjects with high amyloid load progressed to either MCI or AD. These subjects had significantly lower memory scores in the presence of higher baseline [^{11}C]PIB retention and higher uptake at follow-up compared with those subjects who remained cognitively stable. Interestingly, one of the 73 [^{11}C]PIB-negative subjects showed cognitive decline during the 3 years.[57] Although the prediction is that an asymptomatic elderly individual with low [^{11}C]PIB binding is less likely to convert to AD than a [^{11}C]PIB-positive individual, the predictive value of [^{11}C]PIB remains to be determined. This suggests that other insults besides Aβ load may play a role in the cognitive deterioration in these individuals. Moreover, there is no description of an amyloid plaque-only dementia, whilst tau-only pathology can cause neuronal loss in tauopathies such as FTLD.[42] Since post-mortem analysis is required to ascertain the diagnosis of AD, a [^{11}C]PIB-negative scan might represent a misdiagnosed case, i.e. the cause of dementia might be due to non-AD-related processes. The other highly speculative explanations include lack of Aβ plaques or reduced uptake of [^{11}C]PIB, reduced affinity for [^{11}C]PIB for the Aβ plaques in a given individual, or a substance (e.g. medication) interfering with the binding. At present, there is no evidence to favour any of the explanations.[61] It can be suggested that Aβ oligomers might be mediating the toxicity at some distance from the established plaques. Moreover, they could subtly damage and predispose sensitive neurons to the development of intracellular tau aggregates.[42] The dilemma regarding oligomers is that its definition is misleading. In recent years, due to the lack of correlation between amyloid plaques and cognitive measures, the culprit is thought to be the amyloid oligomers; however, this assumption needs to be ascertained. To date, there is no mechanism to image amyloid oligomers, and the role of these oligomers in the disease pathogenesis needs to be elucidated.

Of particular note is the fact that although most [^{11}C]PIB-positive elderly subjects have subtle cognitive deterioration and are likely to develop AD, nevertheless few [^{11}C]PIB-positive individuals remain cognitively intact.[64] Recently, studies have found that higher educational attainment as well as exercise may permit individuals with pre-clinical AD, as determined by [^{11}C]PIB-PET, to withstand the AD pathology in the absence of any overt cognitive impairment compared with individuals with less education.[70–73] It is suggested that individuals with higher educational training have a greater cognitive reserve, or compensatory approaches that enable protection against the clinical expression of AD. Taken together, amyloid deposition is associated with cognitive deterioration both in AD and in normal elderly subjects but the association is modified by the cognitive reserve.[70,72]

Relationship between amyloid and glucose metabolism

Several reports have examined the relationship between amyloid load and glucose metabolism, with some reporting no association between

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[^{11}C]PIB and [^{18}F]FDG,[74] whilst others observing inverse correlation between the two tracers in the temporoparietal cortex.[75] However, no correlations between [^{11}C]PIB and [^{18}F]FDG have been found in the frontal cortex.[11,26] Braak staging scheme suggests that the frontal neurofibrillary tangles are formed relatively late in the disease process, whereas frontal amyloid deposition occurs much earlier.[29,76] Since [^{18}F]FDG reflects neuronal function and in turn synaptic activity,[77] it is probably influenced more by intraneuronal tangle formation as opposed to extracellular plaque formation. For example, [^{18}F]FDG studies show a characteristic pattern of temporoparietal and posterior cingulate hypometabolism with hippocampus being one of the earliest regions[78,79] to experience functional changes in addition to tau tangle pathology in AD and MCI. The lack of dissociation between amyloid load and glucose metabolism raises questions about the exact role of plaque formation in the destruction of neurons.

Comparative analysis of [^{11}C]PIB and [^{18}F]FDG demonstrated that [^{11}C]PIB was more accurate in differentiating AD from FTLD.[80] Moreover, Aβ imaging outperformed [^{18}FDG] at identifying MCI subtypes. Reports from a meta-analysis suggest that amyloid and [^{18}F]FDG imaging are potentially valuable techniques for prediction of progress in MCI subjects and their combined use is a promising option for prediction purposes depending on availability and experience.

Relationship between amyloid imaging and CSF markers

Recent studies have suggested that amyloid imaging and CSF markers can be used to detect the presence of Aβ deposits as early as 10–15 years prior to the onset of cognitive decline owing to AD.[82–85] Moreover, evidence of neurodegeneration and tauopathy appears to begin 5 years prior to the cognitive decline characterizing early AD.[82–85] In order to conduct preventative clinical trials to delay the onset of cognitive impairment and dementia, biomarkers need to be utilized to select subjects who are clinically normal but at high risk for near-term cognitive decline.[86] The CSF markers Aβ42, total tau protein, and tau phosphorylated at threonine 181 are gradually finding their way into routine clinical practice as an affirmative diagnostic tool for AD.[87–89] These biomarkers have been implemented in the revised diagnostic criteria for AD and the combination of CSF markers mentioned above leads to high levels (around 80%) of sensitivity, specificity and diagnostic accuracy for discrimination between AD and controls, and can also be used to diagnose MCI subjects. In AD, the typical CSF profile is low Aβ42 and high total tau and phosphorylated tau.[90] This is because slower Aβ clearance from the brain putatively leads to increased Aβ deposition in the brain and lower CSF Aβ42 concentrations.[91,92] Some studies found no correlation between [^{11}C]PIB retention and CSF total tau or phosphorylated tau,[81,93] whilst others reported a strong inverse correlation between Aβ deposition in the brain as measured by [^{11}C]PIB and CSF Aβ42.[49,50,85,94–96] However, increased [^{11}C]PIB retention along with low CSF Aβ was detected in cognitively non-demented individuals supposedly reflecting Aβ deposition, years before the clinical manifestation of AD phenotype.[27,53,61,85,96] Large population studies would be required to further evaluate the prognostic value of Aβ imaging and CSF assessments as antecedent AD biomarkers.

Amyloid imaging and MRI atrophy

Studies have found a strong correlation between [^{11}C]PIB and hippocampal atrophy as measured by MRI. For example, Bourgeat *et al.* demonstrated that in a [^{11}C]PIB-positive healthy control group, pronounced atrophy was observed in the inferior temporal neocortex, which suggests that Aβ deposition in the aforementioned region is related to hippocampal synaptic and neuronal degeneration.[97–99] Furthermore, data suggest that the relationship between Aβ deposition and cortical atrophy is sequential, where Aβ load pre-dates synaptic dysfunction and neuro-degeneration.[98,100] Subsequently, the amyloid-based disruption of neuronal integrity might contribute to the regional expansion of neuronal dysfunction and this is later manifested as structural changes evident on MRI scans.[99,100] One study did not find a correlation between atrophy trajectories and [^{11}C]PIB uptake in cognitively normal elderly individuals.[101] However, Chetelat and co-workers found that subjects with high Aβ deposition showed a significantly higher rate of atrophy in the temporal as well as posterior cingulate cortices relative to individuals with low Aβ burden.[102]

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Amyloid imaging in Lewy body disorders

The neuropathological hallmarks of dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD) are characterized by the presence of subcortical and/or cortical Lewy bodies. It has become increasingly known that substantial amyloid pathology is a feature of the disease process with 30–85% of DLB cases and 15–100% of PDD cases showing [^{11}C]PIB positivity, respectively.[27,103–106] Most studies conducted in DLB and PDD cases *in vivo* have found higher amyloid plaques in DLB cases compared with PDD and non-demented PD cases. [^{11}C]PIB positivity in a few studies was associated with greater cognitive impairment and a rapid disease progression.[103,106] Edison *et al.*[103] demonstrated that 85% (11/13) of DLB subjects had significantly increased amyloid burden in one or more cortical regions whilst 83% (10/12) of PDD subjects had a normal [^{11}C]PIB scan. Interestingly, cortical [^{11}C]PIB binding in PDD was comparable to that of PD and healthy control subjects. It is reported that none of the PD cases showed any evidence of increased [^{11}C]PIB retention. Consistent with previous report, Gomperts *et al.*[105] demonstrated that cortical [^{11}C]PIB load was higher in DLB than in PDD but comparable to AD. Provided the high frequency of amyloid plaques and a higher incidence of [^{11}C]PIB-positive scans in DLB, it is unlikely that the amyloid scans will be of any help in differentiating between DLB and AD. Nevertheless, amyloid imaging may differentiate PD or PDD from AD and DLB but often this differentiation can be accomplished clinically.

Together, the above findings suggest that global cortical [^{11}C]PIB retention is high in DLB, but low and infrequent in PDD. Increased fibrillar amyloid deposition might contribute to the rapid progression of dementia in DLB, and it may also play a significant role with respect to timing of dementia relative to the cardinal motor symptoms of Parkinsonism in DLB and PDD.[105,107]

Amyloid imaging in frontotemporal dementia and other dementia subtypes

FTLD is a non-specific, umbrella term to describe disorders associated with degeneration of the frontal and anterior temporal lobes.[108] It encompasses a wide range of clinical syndromes including the behavioural variant of fronto-temporal dementia, frontotemporal dementia with motor-neuron disease, and the semantic and non-fluent variants of primary progressive aphasia (PPA).[109,110] FTLD and AD represent the leading causes of early age of onset dementia with similar occurrence rates in subjects younger than the age of 65.[111] Due to the strikingly analogous clinical and anatomical overlap, distinguishing between the two during life can be difficult, and misdiagnosis rates of 10–40% have been documented.[112] Since amyloid deposition is not a defining neuropathological feature of FTLD, [^{11}C]PIB imaging can be used to differentiate FTLD from AD. Studies have convincingly shown [^{11}C]PIB binding in FTLD to be comparable to healthy controls, a pattern that is significantly different from AD.[27,113]

Amyloid deposition is also a neuropathological marker of other dementias such as posterior cortical atrophy (PCA) and cerebral amyloid angiopathy (CAA).[114] CAA subjects show a relatively increased [^{11}C]PIB load in the occipital cortex, in keeping with post-mortem data.[115] Furthermore, [^{11}C]PIB can be used to distinguish or rule out the atypical presentations of AD in clinical syndromes associated with non-Aβ pathology including Prion disease.[30] Single case studies have found an asymmetric left hemisphere [^{11}C]PIB uptake in PPA and posterior-predominant uptake in PCA. However, group analysis revealed [^{11}C]PIB uptake values in PPA and PCA to be diffuse, symmetric and indistinguishable from the pattern observed in AD, and no correlation was found with clinical phenotype. In the clinic, non-amnestic presentations of AD are a relatively common finding at specialized dementia referral centres.[30] The continued use of [^{11}C]PIB or other [^{18}F] amyloid tracers in development will help to select subjects with atypical clinical symptoms who may be ideal candidates for anti-Aβ therapies.

[^{18}F]-labelled tracers

FDDNP

The first human study with [^{18}F]-FDDNP was in nine patients with early AD and seven similar age controls.[10] This study found high ^{18}F-FDDNP binding in the hippocampus, and temporal, parietal and frontal regions compared with the controls. Tracer retention was increased 10–15% above baseline in frontal, temporal and parietal cortex,

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regions that typically show both Aβ plaques and neurofibrillary tangles (NFTs). A unique feature of FDDNP is its ability for structural recognition of β-sheet aggregate conformations in neuroaggregates (e.g. β-amyloid, tau and prions) – like Congo Red and thioflavin-T.[116] However, in addition to amyloid plaques, FDDNP binds to NFTs. Despite the proven advantages of FDDNPs, there are also some limitations to its wider use. One particular limitation of FDDNP is the small cortical signal difference between control and AD subjects.[117] Another limitation of FDDNP is that it does not bind selectively to β-amyloid plaques, although this would assume that β-amyloid is the principal cause of AD. In addition there is evidence to suggest that FDDNP binding can be disrupted by commonly used non-steroidal anti-inflammatory drugs.[118]

FDDNP and PIB have different binding properties and distinct advantages and disadvantages. FDDNP binds to both Aβ and tau amyloid conformations, and thus accounts for the full spectrum of AD pathology,[30] whereas PIB appears to be highly specific for Aβ amyloid, which makes it a better tracer for diagnostically discriminating between AD and non-Aβ dementias.[27,119] A direct comparison of FDDNP and PIB-PET in the same subjects (14 AD, 11 MCI and 13 controls) found an almost 10-fold higher binding potential in AD for PIB compared with FDDNP.[120] Of the two tracers, only PIB has been quantitatively validated *in vivo* compared with autopsy.[121,122] Published reports of FDDNP have so far originated in three centres and include a limited number of subjects, whereas PIB studies have been performed in large numbers around the globe.[30]

Flutemetamol

Although [^{11}C]PIB has been the most widely used amyloid tracer, its availability for use is somewhat limited because of a short half-life of 20 min. To overcome this difficulty, [^{18}F] tracers, which have a half-life of 110 min, have been developed and can be used in PET centres where a cyclotron is not on-site. [^{18}F]flutemetamol, unlike other [^{18}F] amyloid tracers, has the advantage that there has been extensive work done on its parent molecule, [^{11}C]PiB, which can easily lend itself to the validation of [^{18}F]flutemetamol. Studies utilizing [^{18}F]flutemetamol have shown that it can differentiate between AD and healthy control subjects, and its spatial distribution closely resembles that of [^{11}C]PIB.[123,124] However, white matter and pons showed increased uptake of [^{18}F]flutemetamol compared with [^{11}C]PIB, possibly due to greater non-specific binding, but this did not lead to misclassification of scans.[124]

Florbetaben

[^{11}F]Florbetaben (also known as AV-1) has a distinct advantage over other [^{18}F] tracers including [^{18}F]flutemetamol in that it causes a much lower radiation burden[15] and has a good safety profile with high initial uptake and rapid washout kinetics.[125] [^{11}F]Florbetaben has demonstrated specific binding to neuritic Aβ plaques and to cerebral amyloid angiopathy, but does not bind to Lewy bodies, glial cytoplasmic inclusions, α-synuclein, NFTs or other tau pathology, to any considerable extent.[126] More importantly, it has been shown that [^{18}F]Florbetaben PET imaging is able to discriminate between AD, healthy controls and FTLD subjects, at a level comparable to [^{11}C]PIB.[127,128]

Florbetapir

[^{18}F]Florbetapir (Amyvid) is the first Food and Drug Administration (FDA)-approved radiotracer for detection of amyloid plaques *in vivo* due to its favourable kinetics and high selectivity for Aβ plaques, comparable to [^{11}C]PIB. Moreover, *in vitro* autoradiography of post-mortem human brain tissues and *ex vivo* autoradiography of transgenic mouse brain demonstrated selective binding of [^{18}F]florbetapir to Aβ plaques but not NFTs.[129,130] [^{18}F]Florbetapir has consistently demonstrated a high discriminatory power in being able to successfully differentiate between AD subjects, MCI subjects with amyloid-positive and amyloid-negative scans, and healthy controls.[131,132]

Conclusion and future directions

[^{11}C]PIB-PET studies support a model in which amyloid aggregation is an early event that occurs insidiously and precedes cognitive impairment and brain atrophy. Dementia is an age-dependent process; for example, amyloid is thought to be

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present in around 20% of healthy 65-year-olds but subjects over the age of 85 years have an 85% chance of acquiring dementia. This suggests that as an individual ages, the prevalence of getting clinical AD in the population rises exponentially.[39,133] By the time subjects reach a stage of MCI, amyloid accumulation already approximates that of AD, a process that takes around a couple of decades to develop.[39] In the face of these changes, the cognitive reserve or compensatory mechanisms spring into action to cope with the accruing pathological stress. Once the brain's adaptive plasticity mechanisms have been exhausted, subjects inevitably progress to mild dementia followed by accelerated clinical decline and neurodegeneration (as reflected by MRI and FDG-PET). The downstream events might occur independently of amyloid accumulation, which has reached a plateau or continues to progress very slowly. Additionally, although present, the protective role of education seems to diminish among participants with greater frequency of neurofibrillary tangles. Taken together, this suggests that the association between education and dementia may differ, depending on the type and extent of neuropathology.[70] Once a threshold is surpassed and tau hyperphosphorylation occurs, then cognitive decline is observed. Therefore, it is important to highlight the need to quantify cognitive reserve in dementia research to delineate the effect of the brain's neuroplasticity on neurodegeneration and neuroinflammation.

Furthermore, to fully comprehend the predictive potential of [^{11}C]PIB imaging, studies would need to investigate the direct relationship between [^{11}C]PIB binding and neuropathology observed in dementia. Amyloid imaging data thus far has been derived mostly from cross-sectional studies and would need to be verified by longitudinal studies. In addition, [^{11}C]PIB binds only to fibrillar amyloid plaques, and apparent dissociations between [^{11}C]PIB uptake and other disease measures may be accounted for by the soluble forms of Aβ that are not reflected by [^{11}C]PIB-PET.[30] Based on the working model of amyloid aggregation, it appears that the optimal time to initiate therapies targeting Aβ may be in the pre-MCI stages when cognition is still intact and neurodegeneration is mild. By the time patients progress to MCI and AD, other downstream effects might be in motion, and the therapeutic window of opportunity to administer anti-amyloid therapies may already be lost.

In conclusion, PET amyloid tracers are promising biomarkers for early detection of AD pathology. A number of promising [^{18}F]-labelled imaging tracers are currently under development, which will allow wider application of amyloid imaging to clinical practice and research. The development of *in vivo* biomarkers for other critical elements of AD pathogenesis such as soluble Aβ oligomers, tau, acetylcholine and brain inflammation would further inform our understanding of the disease and assist in developing and testing disease-modifying and perhaps preventative treatment for AD.

Conflicts of interest

None declared.

References

1 Thal DR, Rub U, Orantes M, Braak H. Phases of A beta-deposition in the human brain and its relevance for the development of AD. *Neurology* 2002; **58**: 1791–800.
2 McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1984; **34**: 939–44.
3 McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; **7**: 263–69.
4 Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999; **56**: 303–8.
5 Tierney JP, Snow WG, Fisher RH, Nores A, Nadon G, Dunn E, George-Hyslop PH. Prediction of probable Alzheimer's disease in memory-impaired patients: A prospective longitudinal study. *Neurology* 1996; **46**: 661–65.
6 Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B. Current concepts in mild cognitive impairment. *Arch Neurol* 2001; **58**: 1985–92.

https://doi.org/10.1017/S0959259812000160 Published online by Cambridge University Press

7 Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science* 2002; **297**: 353–56.

8 Klunk WE. Amyloid imaging as a biomarker for cerebral beta-amyloidosis and risk prediction for Alzheimer dementia. *Neurobiol Aging* 2011; **32** (suppl 1): S20–36.

9 Herholz K, Carter SF, Jones M. Positron emission tomography imaging in dementia. *Br J Radiol* 2007; **80** (spec no 2): S160–67.

10 Shoghi-Jadid K, Small GW, Agdeppa ED, Kepe V, Ercoli LM, Siddarth P, Read S, Satyamurthy N, Petric A, Huang SC, Barrio JR. Localization of neurofibrillary tangles and beta-amyloid plaques in the brains of living patients with Alzheimer disease. *Am J Geriatr Psychiat* 2002; **10**: 24–35.

11 Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, Bergström M, Savitcheva I, Huang GF, Estrada S, Ausén B, Debnath ML, Barletta J, Price JC, Sandell J, Lopresti BJ, Wall A, Koivisto P, Antoni G, Mathis CA, Långström B. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Annals Neurol* 2004; **55**: 306–19.

12 Nyberg S, Jönhagen ME, Cselényi Z, Halldin C, Julin P, Olsson H, Freund-Levi Y, Andersson J, Varnäs K, Svensson S, Farde L. Detection of amyloid in Alzheimer's disease with positron emission tomography using [^{11}C]AZD2184. *Eur J Nucl Med Mol Imaging* 2009; **36**: 1859–63.

13 Kudo Y, Okamura N, Furumoto S, Tashiro M, Furukawa K, Maruyama M, Itoh M, Iwata R, Yanai K, Arai H. 2-(2-[2-Dimethylamino-thiazol-5-yl]ethenyl)-6-(2-[fluoro]ethoxy)benzoxazole: a novel PET agent for in vivo detection of dense amyloid plaques in Alzheimer's disease patients. *J Nucl Med* 2007; **48**: 553–61.

14 Verhoeff NP, Wilson AA, Takeshita S, Trop L, Hussey D, Singh K, Kung HF, Kung MP, Houle S. In-vivo imaging of Alzheimer disease beta-amyloid with [^{11}C]SB-13 PET. *Am J Geriatr Psychiat* 2004; **12**: 584–95.

15 Koole M, Lewis DM, Buckley C, Nelissen N, Vandenbulcke M, Brooks DJ, Vandenberghe R, Van Laere K. Whole-body biodistribution and radiation dosimetry of 18F-GE067: a radioligand for in vivo brain amyloid imaging. *J Nucl Med* 2009; **50**: 818–22.

16 Rowe CC, Ackerman U, Browne W, Mulligan R, Pike KL, O'Keefe G, Tochon-Danguy H, Chan G, Berlangieri SU, Jones G, Dickinson-Rowe KL, Kung HP, Zhang W, Kung MP, Skovronsky D, Dyrks T, Holl G, Krause S, Friebe M, Lehman L, Lindemann S, Dinkelborg LM, Masters CL, Villemagne VL. Imaging of amyloid beta in Alzheimer's disease with 18F-BAY94–9172, a novel PET tracer: proof of mechanism. *Lancet Neurol* 2008; **7**: 129–35.

17 Zhang W, Oya S, Kung MP, Hou C, Maier DL, Kung HF. F-18 Polyethyleneglycol stilbenes as PET imaging agents targeting Abeta aggregates in the brain. *Nucl Med Biol* 2005; **32**: 799–809.

18 Juréus A, Swahn BM, Sandell J, Jeppsson F, Johnson AE, Johnström P, Neelissen JA, Sunnemark D, Farde L, Svensson SP. Characterization of AZD4694, a novel fluorinated Abeta plaque neuroimaging PET radioligand. *J Neurochem* 2010; **114**: 784–94.

19 Cselényi Z, Jönhagen ME, Forsberg A, Halldin C, Julin P, Schou M, Johnström P, Varnäs K, Svensson S, Farde L. Clinical validation of 18F-AZD4694, an amyloid-beta-specific PET radioligand. *J Nucl Med* 2012; **53**: 415–24.

20 Klunk WE, Wang Y, Huang GF, Debnath ML, Holt DP, Shao L, Hamilton RL, Ikonomovic MD, DeKosky ST, Mathis CA. The binding of 2-(4'-methylaminophenyl)benzothiazole to postmortem brain homogenates is dominated by the amyloid component. *J Neurosci* 2003; **23**: 2086–92.

21 Lockhart A, Ye L, Judd DB, Merritt AT, Lowe PN, Morgenstern JL, Hong G, Gee AD, Brown J. Evidence for the presence of three distinct binding sites for the thioflavin T class of Alzheimer's disease PET imaging agents on beta-amyloid peptide fibrils. *J Biol Chem* 2005; **280**: 7677–84.

22 Fodero-Tavoletti MT, Smith DP, McLean CA, Adlard PA, Barnham KJ, Foster LE, Leone L, Perez K, Cortés M, Culvenor JG, Li QX, Laughton KM, Rowe CC, Masters CL, Cappai R, Villemagne VL. In vitro characterization of Pittsburgh compound-B binding to Lewy bodies. *J Neurosci* 2007; **27**: 10365–71.

23 Ye L, Velasco A, Fraser G, Beach TG, Sue L, Osredkar T, Libri V, Spillantini MG, Goedert M, Lockhart A. In vitro high affinity alpha-synuclein binding sites for the amyloid imaging agent PIB are not matched by binding to Lewy bodies in postmortem human brain. *J Neurochem* 2008; **105**: 1428–37.

24 Mathis CA, Lopresti BJ, Klunk WE. Impact of amyloid imaging on drug development in Alzheimer's disease. *Nuclear Med Biol* 2007; **34**: 809–22.

25 Jack CR Jr, Lowe VJ, Senjem ML, Weigand SD, Kemp BJ, Shiung MM, Knopman DS, Boeve BF, Klunk WE, Mathis CA, Petersen RC. 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and

https://doi.org/10.1017/S0959259812000160 Published online by Cambridge University Press

amnestic mild cognitive impairment. *Brain* 2008; **131**: 665–80.
26 Edison P, Archer HA, Hinz R, Hammers A, Pavese N, Tai YF, Hotton G, Cutler D, Fox N, Kennedy A, Rossor M, Brooks DJ. Amyloid, hypometabolism, and cognition in Alzheimer disease: an [11C]PIB and [18F]FDG PET study. *Neurology* 2007; **68**: 501–8.
27 Rowe CC, Ng S, Ackermann U, Gong SJ, Pike K, Savage G, Cowie TF, Dickinson KL, Maruff P, Darby D, Smith C, Woodward M, Merory J, Tochon-Danguy H, O'Keefe G, Klunk WE, Mathis CA, Price JC, Masters CL, Villemagne VL. Imaging beta-amyloid burden in aging and dementia. *Neurology* 2007; **68**: 1718–25.
28 Kemppainen NM, Aalto S, Wilson IA, Någren K, Helin S, Brück A, Oikonen V, Kailajärvi M, Scheinin M, Viitanen M, Parkkola R, Rinne JO. Voxel-based analysis of PET amyloid ligand [11C]PIB uptake in Alzheimer disease. *Neurology* 2006; **67**: 1575–80.
29 Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol* 1991; **82**: 239–59.
30 Rabinovici GD, Jagust WJ. Amyloid imaging in aging and dementia: testing the amyloid hypothesis in vivo. *Behav Neurol* 2009; **21**: 117–28.
31 Lopresti BJ, Klunk WE, Mathis CA, Hoge JA, Ziolko SK, Lu X, Meltzer CC, Schimmel K, Tsopelas ND, DeKosky ST, Price JC. Simplified quantification of Pittsburgh Compound B amyloid imaging PET studies: a comparative analysis. *J Nucl Med* 2005; **46**: 1959–72.
32 Price JC, Klunk WE, Lopresti BJ, Lu X, Hoge JA, Ziolko SK, Holt DP, Meltzer CC, DeKosky ST, Mathis CA. Kinetic modeling of amyloid binding in humans using PET imaging and Pittsburgh Compound-B. *J Cereb Blood Flow Metab* 2005; **25**: 1528–47.
33 Watanabe R, Duchen LW. Cerebral amyloid in human prion disease. *Neuropathol Appl Neurobiol* 1993; **19**: 253–60.
34 Mead S, Poulter M, Beck J, Webb TE, Campbell TA, Linehan JM, Desbruslais M, Joiner S, Wadsworth JD, King A, Lantos P, Collinge J. Inherited prion disease with six octapeptide repeat insertional mutation–molecular analysis of phenotypic heterogeneity. *Brain* 2006; **129**: 2297–317.
35 Klunk WE, Price JC, Mathis CA, Tsopelas ND, Lopresti BJ, Ziolko SK, Bi W, Hoge JA, Cohen AD, Ikonomovic MD, Saxton JA, Snitz BE, Pollen DA, Moonis M, Lippa CF, Swearer JM, Johnson KA, Rentz DM, Fischman AJ, Aizenstein HJ, DeKosky ST. Amyloid deposition begins in the striatum of presenilin-1 mutation carriers from two unrelated pedigrees. *J Neurosci* 2007; **27**: 6174–84.
36 Edison P, Hinz R, Ramlackhansingh A, Thomas J, Gelosa G, Archer HA, Turkheimer FE, Brooks DJ. Can target-to-pons ratio be used as a reliable method for the analysis of [^{11}C]PIB brain scans? *Neuroimage* 2012; **60**: 1716–23.
37 Weiner MW, Veitch DP, Aisen PS, Beckett LA, Cairns NJ, Green RC, Harvey D, Jack CR, Jagust W, Liu E, Morris JC, Petersen RC, Saykin AJ, Schmidt ME, Shaw L, Siuciak JA, Soares H, Toga AW, Trojanowski JQ. The Alzheimer's Disease Neuroimaging Initiative: A review of papers published since its inception. *Alzheimers Dement* 2012; **8** (suppl 1): S1–68.
38 Engler H, Forsberg A, Almkvist O, Blomquist G, Larsson E, Savitcheva I, Wall A, Ringheim A, Långström B, Nordberg A. Two-year follow-up of amyloid deposition in patients with Alzheimer's disease. *Brain* 2006; **129**: 2856–66.
39 Jack CR Jr, Lowe VJ, Weigand SD, Wiste HJ, Senjem ML, Knopman DS, Shiung MM, Gunter JL, Boeve BF, Kemp BJ, Weiner M, Petersen RC; Alzheimer's Disease Neuroimaging Initiative. Serial PIB and MRI in normal, mild cognitive impairment and Alzheimer's disease: implications for sequence of pathological events in Alzheimer's disease. *Brain* 2009; **132**: 1355–65.
40 Scheinin NM, Aalto S, Koikkalainen J, Lötjönen J, Karrasch M, Kemppainen N, Viitanen M, Någren K, Helin S, Scheinin M, Rinne JO. Follow-up of [11C]PIB uptake and brain volume in patients with Alzheimer disease and controls. *Neurology* 2009; **73**: 1186–92.
41 Kadir A, Almkvist O, Forsberg A, Wall A, Engler H, Långström B, Nordberg A. Dynamic changes in PET amyloid and FDG imaging at different stages of Alzheimer's disease. *Neurobiol Aging* 2010; **33**: 198, e1–14.
42 Benilova I, Karran E, De Strooper B. The toxic Abeta oligomer and Alzheimer's disease: an emperor in need of clothes. *Nat Neurosci* 2012; **15**: 349–57.
43 Koffie RM, Meyer-Luehmann M, Hashimoto T, Adams KW, Mielke ML, Garcia-Alloza M, Micheva KD, Smith SJ, Kim ML, Lee VM, Hyman BT, Spires-Jones TL. Oligomeric amyloid beta associates with postsynaptic densities and correlates with excitatory synapse loss near senile plaques. *Proc Natl Acad Sci USA* 2009; **106**: 4012–17.
44 Yan P, Bero AW, Cirrito JR, Xiao Q, Hu X, Wang Y, Gonzales E, Holtzman DM, Lee JM. Characterizing the appearance and growth of

https://doi.org/10.1017/S0959259812000160 Published online by Cambridge University Press

amyloid plaques in APP/PS1 mice. *J Neurosci* 2009; **29**: 10706–14.
45 Meyer-Luehmann M, Spires-Jones TL, Prada C, Garcia-Alloza M, de Calignon A, Rozkalne A, Koenigsknecht-Talboo J, Holtzman DM, Bacskai BJ, Hyman BT. Rapid appearance and local toxicity of amyloid-beta plaques in a mouse model of Alzheimer's disease. *Nature* 2008; **451**: 720–24.
46 Okello A, Edison P, Archer HA, Turkheimer FE, Kennedy J, Bullock R, Walker Z, Kennedy A, Fox N, Rossor M, Brooks DJ. Microglial activation and amyloid deposition in mild cognitive impairment: a PET study. *Neurology* 2009; **72**: 56–62.
47 Kemppainen NM, Aalto S, Wilson IA, Någren K, Helin S, Brück A, Oikonen V, Kailajärvi M, Scheinin M, Viitanen M, Parkkola R, Rinne JO. PET amyloid ligand [11C]PIB uptake is increased in mild cognitive impairment. *Neurology* 2007; **68**: 1603–6.
48 Mormino EC, Kluth JT, Madison CM, Rabinovici GD, Baker SL, Miller BL, Koeppe RA, Mathis CA, Weiner MW, Jagust WJ; Alzheimer's Disease Neuroimaging Initiative. Episodic memory loss is related to hippocampal-mediated beta-amyloid deposition in elderly subjects. *Brain* 2009; **132**: 1310–23.
49 Koivunen J, Pirttilä T, Kemppainen N, Aalto S, Herukka SK, Jauhianen AM, Hänninen T, Hallikainen M, Någren K, Rinne JO, Soininen H. PET amyloid ligand [11C]PIB uptake and cerebrospinal fluid beta-amyloid in mild cognitive impairment. *Dement Geriatr Cogn Disord* 2008; **26**: 378–83.
50 Forsberg A, Engler H, Almkvist O, Blomquist G, Hagman G, Wall A, Ringheim A, Långström B, Nordberg A. PET imaging of amyloid deposition in patients with mild cognitive impairment. *Neurobiol Aging* 2008; **29**: 1456–65.
51 Pike KE, Savage G, Villemagne VL, Ng S, Moss SA, Maruff P, Mathis CA, Klunk WE, Masters CL, Rowe CC. Beta-amyloid imaging and memory in non-demented individuals: evidence for preclinical Alzheimer's disease. *Brain* 2007; **130**: 2837–44.
52 Okello A, Koivunen J, Edison P, Archer HA, Turkheimer FE, Någren K, Bullock R, Walker Z, Kennedy A, Fox NC, Rossor MN, Rinne JO, Brooks DJ. Conversion of amyloid positive and negative MCI to AD over 3 years: an 11C-PIB PET study. *Neurology* 2009; **73**: 754–60.
53 Aizenstein HJ, Nebes RD, Saxton JA, Price JC, Mathis CA, Tsopelas ND, Ziolko SK, James JA, Snitz BE, Houck PR, Bi W, Cohen AD, Lopresti BJ, DeKosky ST, Halligan EM, Klunk WE. Frequent amyloid deposition without significant cognitive impairment among the elderly. *Arch Neurol* 2008; **65**: 1509–17.
54 Mormino EC, Brandel MG, Madison CM, Rabinovici GD, Marks S, Baker SL, Jagust WJ. Not quite PIB-positive, not quite PIB-negative: slight PIB elevations in elderly normal control subjects are biologically relevant. *Neuroimage* 2011; **59**: 1152–60.
55 Koivunen J, Scheinin N, Virta JR, Aalto S, Vahlberg T, Någren K, Helin S, Parkkola R, Viitanen M, Rinne JO. Amyloid PET imaging in patients with mild cognitive impairment: a 2-year follow-up study. *Neurology* 2011; **76**: 1085–90.
56 Jagust WJ, Bandy D, Chen K, Foster NL, Landau SM, Mathis CA, Price JC, Reiman EM, Skovronsky D, Koeppe RA; Alzheimer's Disease Neuroimaging Initiative. The Alzheimer's Disease Neuroimaging Initiative positron emission tomography core. *Alzheimers Dement* 2010; **6**: 221–29.
57 Villemagne VL, Pike KE, Chételat G, Ellis KA, Mulligan RS, Bourgeat P, Ackermann U, Jones G, Szoeke C, Salvado O, Martins R, O'Keefe G, Mathis CA, Klunk WE, Ames D, Masters CL, Rowe CC. Longitudinal assessment of Abeta and cognition in aging and Alzheimer disease. *Ann Neurol* 2011; **69**: 181–92.
58 Ossenkoppele R, van Berckel BN, Prins ND. Amyloid imaging in prodromal Alzheimer's disease. *Alzheimers Res Ther* 2011; **3**: 26.
59 Wolk DA, Klunk W. Update on amyloid imaging: from healthy aging to Alzheimer's disease. *Curr Neurol Neurosci Rep* 2009; **9**: 345–52.
60 Price JL, Morris JC. Tangles and plaques in non-demented aging and 'preclinical' Alzheimer's disease. *Ann Neurol* 1999; **45**: 358–68.
61 Mintun MA, Larossa GN, Sheline YI, Dence CS, Lee SY, Mach RH, Klunk WE, Mathis CA, DeKosky ST, Morris JC. [11C]PIB in a non-demented population: potential antecedent marker of Alzheimer disease. *Neurology* 2006; **67**: 446–52.
62 Reiman EM, Chen K, Liu X, Bandy D, Yu M, Lee W, Ayutyanont N, Keppler J, Reeder SA, Langbaum JB, Alexander GE, Klunk WE, Mathis CA, Price JC, Aizenstein HJ, DeKosky ST, Caselli RJ. Fibrillar amyloid-beta burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. *Proc Natl Acad Sci USA* 2009; **106**: 6820–25.
63 Villemagne VL, Pike KE, Darby D, Maruff P, Savage G, Ng S, Ackermann U, Cowie TF, Currie J, Chan SG, Jones G, Tochon-Danguy H, O'Keefe G, Masters CL, Rowe CC. Abeta deposits in older non-demented individuals with cognitive decline

https://doi.org/10.1017/S0959259812000160 Published online by Cambridge University Press

are indicative of preclinical Alzheimer's disease. *Neuropsychologia* 2008; **46**: 1688–97.
64 Rodrigue KM, Kennedy KM, Devous MD Sr, Rieck JR, Hebrank AC, Diaz-Arrastia R, Mathews D, Park DC. Beta-Amyloid burden in healthy aging: regional distribution and cognitive consequences. *Neurology* 2012; **78**: 387–95.
65 Sojkova J, Zhou Y, An Y, Kraut MA, Ferrucci L, Wong DF, Resnick SM. Longitudinal patterns of beta-amyloid deposition in nondemented older adults. *Arch Neurol* 2011; **68**: 644–49.
66 Bennett DA, Schneider JA, Arvanitakis Z, Kelly JF, Aggarwal NT, Shah RC, Wilson RS. Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology* 2006; **66**: 1837–44.
67 Kantarci K, Lowe V, Przybelski SA, Weigand SD, Senjem ML, Ivnik RJ, Preboske GM, Roberts R, Geda YE, Boeve BF, Knopman DS, Petersen RC, Jack CR Jr. APOE modifies the association between Abeta load and cognition in cognitively normal older adults. *Neurology* 2012; **78**: 232–40.
68 Vlassenko AG, Mintun MA, Xiong C, Sheline YI, Goate AM, Benzinger TL, Morris JC. Amyloid-beta plaque growth in cognitively normal adults: longitudinal [11C]Pittsburgh compound B data. *Ann Neurol* 2011; **70**: 857–61.
69 Bertram L. Alzheimer's genetics in the GWAS era: a continuing story of 'replications and refutations'. *Curr Neurol Neurosci Rep* 2011; **11**: 246–53.
70 Roe CM, Xiong C, Miller JP, Morris JC. Education and Alzheimer disease without dementia: support for the cognitive reserve hypothesis. *Neurology* 2007; **68**: 223–28.
71 Murray AD, Staff RT, McNeil CJ, Salarirad S, Ahearn TS, Mustafa N, Whalley LJ. The balance between cognitive reserve and brain imaging biomarkers of cerebrovascular and Alzheimer's diseases. *Brain* 2011; **134**: 3687–96.
72 Rentz DM, Locascio JJ, Becker JA, Moran EK, Eng E, Buckner RL, Sperling RA, Johnson KA. Cognition, reserve, and amyloid deposition in normal aging. *Ann Neurol* 2010; **67**: 353–64.
73 Tucker AM, Stern Y. Cognitive reserve in aging. *Curr Alzheimer Res* 2011; **8**: 354–60.
74 Furst AJ, Rabinovici GD, Rostomian AH, Steed T, Alkalay A, Racine C, Miller BL, Jagust WJ. Cognition, glucose metabolism and amyloid burden in Alzheimer's disease. *Neurobiol Aging* 2012; **33**: 215–25.
75 Cohen AD, Price JC, Weissfeld LA, James J, Rosario BL, Bi W, Nebes RD, Saxton JA, Snitz BE, Aizenstein HA, Wolk DA, Dekosky ST, Mathis CA, Klunk WE. Basal cerebral metabolism may modulate the cognitive effects of Abeta in mild cognitive impairment: an example of brain reserve. *J Neurosci* 2009; **29**: 14770–78.
76 Braak H, Braak E. Staging of Alzheimer's disease-related neurofibrillary changes. *Neurobiol Aging* 1995; **16**: 271–78; discussion 8–84.
77 Sokoloff L. Relation between physiological function and energy metabolism in the central nervous system. *J Neurochem* 1977; **29**: 13–26.
78 Jagust W, Reed B, Mungas D, Ellis W, Decarli C. What does fluorodeoxyglucose PET imaging add to a clinical diagnosis of dementia? *Neurology* 2007; **69**: 871–77.
79 Mosconi L, Tsui WH, De Santi S, Li J, Rusinek H, Convit A, Li Y, Boppana M, de Leon MJ. Reduced hippocampal metabolism in MCI and AD: automated FDG-PET image analysis. *Neurology* 2005; **64**: 1860–67.
80 Rabinovici GD, Rosen HJ, Alkalay A, Kornak J, Furst AJ, Agarwal N, Mormino EC, O'Neil JP, Janabi M, Karydas A, Growdon ME, Jang JY, Huang EJ, Dearmond SJ, Trojanowski JQ, Grinberg LT, Gorno-Tempini ML, Seeley WW, Miller BL, Jagust WJ. Amyloid vs FDG-PET in the differential diagnosis of AD and FTLD. *Neurology* 2011; **77**: 2034–42.
81 Forsberg A, Almkvist O, Engler H, Wall A, Langstrom B, Nordberg A. High PIB retention in Alzheimer's disease is an early event with complex relationship with CSF biomarkers and functional parameters. *Curr Alzheimer Res* 2010; **7**: 56–66.
82 Perrin RJ, Fagan AM, Holtzman DM. Multimodal techniques for diagnosis and prognosis of Alzheimer's disease. *Nature* 2009; **461**: 916–22.
83 Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol* 2010; **9**: 119–28.
84 Li G, Sokal I, Quinn JF, Leverenz JB, Brodey M, Schellenberg GD, Kaye JA, Raskind MA, Zhang J, Peskind ER, Montine TJ. CSF tau/Abeta42 ratio for increased risk of mild cognitive impairment: a follow-up study. *Neurology* 2007; **69**: 631–39.
85 Fagan AM, Head D, Shah AR, Marcus D, Mintun M, Morris JC, Holtzman DM. Decreased cerebrospinal fluid Abeta(42) correlates with brain atrophy in cognitively normal elderly. *Ann Neurol* 2009; **65**: 176–83.
86 Holtzman DM. CSF biomarkers for secondary prevention trials: why markers of amyloid deposition and neurodegeneration are both important. *Arch Neurol* 2012; **69**: 691–92.
87 Sunderland T, Hampel H, Takeda M, Putnam KT, Cohen RM. Biomarkers in the diagnosis of Alzheimer's disease: are we ready? *J Geriatr Psychiatry Neurol* 2006; **19**: 172–79.

https://doi.org/10.1017/S0959259812000160 Published online by Cambridge University Press

88 Sunderland T, Mirza N, Putnam KT, Linker G, Bhupali D, Durham R, Soares H, Kimmel L, Friedman D, Bergeson J, Csako G, Levy JA, Bartko JJ, Cohen RM. Cerebrospinal fluid beta-amyloid1–42 and tau in control subjects at risk for Alzheimer's disease: the effect of APOE epsilon4 allele. *Biol Psychiatry* 2004; **56**: 670–76.
89 Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, Blennow K, Soares H, Simon A, Lewczuk P, Dean R, Siemers E, Potter W, Lee VM, Trojanowski JQ; Alzheimer's Disease Neuroimaging Initiative. Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects. *Ann Neurol* 2009; **65**: 403–13.
90 Hampel H, Blennow K, Shaw LM, Hoessler YC, Zetterberg H, Trojanowski JQ. Total and phosphorylated tau protein as biological markers of Alzheimer's disease. *Exp Gerontol* 2010; **45**: 30–40.
91 Mawuenyega KG, Sigurdson W, Ovod V, Munsell L, Kasten T, Morris JC, Yarasheski KE, Bateman RJ. Decreased clearance of CNS beta-amyloid in Alzheimer's disease. *Science* 2010; **330**: 1774.
92 Bateman RJ, Munsell LY, Morris JC, Swarm R, Yarasheski KE, Holtzman DM. Human amyloid-beta synthesis and clearance rates as measured in cerebrospinal fluid in vivo. *Nat Med* 2006; **12**: 856–61.
93 Tolboom N, van der Flier WM, Yaqub M, Boellaard R, Verwey NA, Blankenstein MA, Windhorst AD, Scheltens P, Lammertsma AA, van Berckel BN. Relationship of cerebrospinal fluid markers to 11C-PiB and 18F-FDDNP binding. *J Nucl Med* 2009; **50**: 1464–70.
94 Grimmer T, Riemenschneider M, Förstl H, Henriksen G, Klunk WE, Mathis CA, Shiga T, Wester HJ, Kurz A, Drzezga A. Beta amyloid in Alzheimer's disease: increased deposition in brain is reflected in reduced concentration in cerebrospinal fluid. *Biol Psychiatry* 2009; **65**: 927–34.
95 Fagan AM, Mintun MA, Mach RH, Lee SY, Dence CS, Shah AR, LaRossa GN, Spinner ML, Klunk WE, Mathis CA, DeKosky ST, Morris JC, Holtzman DM. Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta42 in humans. *Ann Neurol* 2006; **59**: 512–19.
96 Fagan AM, Roe CM, Xiong C, Mintun MA, Morris JC, Holtzman DM. Cerebrospinal fluid tau/beta-amyloid(42) ratio as a prediction of cognitive decline in nondemented older adults. *Arch Neurol* 2007; **64**: 343–49.
97 Bourgeat P, Chételat G, Villemagne VL, Fripp J, Raniga P, Pike K, Acosta O, Szoeke C, Ourselin S, Ames D, Ellis KA, Martins RN, Masters CL, Rowe CC, Salvado O; AIBL Research Group. Beta-amyloid burden in the temporal neocortex is related to hippocampal atrophy in elderly subjects without dementia. *Neurology* 2010; **74**: 121–27.
98 Chételat G, Villemagne VL, Bourgeat P, Pike KE, Jones G, Ames D, Ellis KA, Szoeke C, Martins RN, O'Keefe GJ, Salvado O, Masters CL, Rowe CC; Australian Imaging Biomarkers and Lifestyle Research Group. Relationship between atrophy and beta-amyloid deposition in Alzheimer disease. *Ann Neurol* 2010; **67**: 317–24.
99 Becker JA, Hedden T, Carmasin J, Maye J, Rentz DM, Putcha D, Fischl B, Greve DN, Marshall GA, Salloway S, Marks D, Buckner RL, Sperling RA, Johnson KA. Amyloid-beta associated cortical thinning in clinically normal elderly. *Ann Neurol* 2011; **69**: 1032–42.
100 Förster S, Grimmer T, Miederer I, Henriksen G, Yousefi BH, Graner P, Wester HJ, Förstl H, Kurz A, Dickerson BC, Bartenstein P, Drzezga A. Regional expansion of hypometabolism in Alzheimer's disease follows amyloid deposition with temporal delay. *Biol Psychiatry* 2012; **71**: 792–97.
101 Driscoll I, Zhou Y, An Y, Sojkova J, Davatzikos C, Kraut MA, Ye W, Ferrucci L, Mathis CA, Klunk WE, Wong DF, Resnick SM. Lack of association between 11C-PiB and longitudinal brain atrophy in non-demented older individuals. *Neurobiol Aging* 2011; **32**: 2123–30.
102 Chételat G, Villemagne VL, Villain N, Jones G, Ellis KA, Ames D, Martins RN, Masters CL, Rowe CC; AIBL Research Group. Accelerated cortical atrophy in cognitively normal elderly with high beta-amyloid deposition. *Neurology* 2012; **78**: 477–84.
103 Edison P, Rowe CC, Rinne JO, Ng S, Ahmed I, Kemppainen N, Villemagne VL, O'Keefe G, Någren K, Chaudhury KR, Masters CL, Brooks DJ. Amyloid load in Parkinson's disease dementia and Lewy body dementia measured with [11C]PIB positron emission tomography. *J Neurol Neurosurg Psychiatry* 2008; **79**: 1331–38.
104 Foster ER, Campbell MC, Burack MA, Hartlein J, Flores HP, Cairns NJ, Hershey T, Perlmutter JS. Amyloid imaging of Lewy body-associated disorders. *Mov Disord* 2010; **25**: 2516–23.
105 Gomperts SN, Rentz DM, Moran E, Becker JA, Locascio JJ, Klunk WE, Mathis CA, Elmaleh DR, Shoup T, Fischman AJ, Hyman BT, Growdon JH, Johnson KA. Imaging amyloid deposition in Lewy body diseases. *Neurology* 2008; **71**: 903–10.
106 Maetzler W, Liepelt I, Reimold M, Reischl G, Solbach C, Becker C, Schulte C, Leyhe T, Keller S,

https://doi.org/10.1017/S0959259812000160 Published online by Cambridge University Press

Melms A, Gasser T, Berg D. Cortical PIB binding in Lewy body disease is associated with Alzheimer-like characteristics. *Neurobiol Dis* 2009; **34**: 107–12.
107 Ballard C, Ziabreva I, Perry R, Larsen JP, O'Brien J, McKeith I, Perry E, Aarsland D. Differences in neuropathologic characteristics across the Lewy body dementia spectrum. *Neurology* 2006; **67**: 1931–34.
108 Rabinovici GD, Miller BL. Frontotemporal lobar degeneration: epidemiology, pathophysiology, diagnosis and management. *CNS Drugs* 2011; **24**: 375–98.
109 Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, Ogar JM, Rohrer JD, Black S, Boeve BF, Manes F, Dronkers NF, Vandenberghe R, Rascovsky K, Patterson K, Miller BL, Knopman DS, Hodges JR, Mesulam MM, Grossman M. Classification of primary progressive aphasia and its variants. *Neurology* 2011; **76**: 1006–14.
110 Laforce R Jr, Rabinovici GD. Amyloid imaging in the differential diagnosis of dementia: review and potential clinical applications. *Alzheimers Res Ther* 2011; **3**: 31.
111 Ratnavalli E, Brayne C, Dawson K, Hodges JR. The prevalence of frontotemporal dementia. *Neurology* 2002; **58**: 1615–21.
112 Alladi S, Xuereb J, Bak T, Nestor P, Knibb J, Patterson K, Hodges JR. Focal cortical presentations of Alzheimer's disease. *Brain* 2007; **130**: 2636–45.
113 Engler H, Santillo AF, Wang SX, Lindau M, Savitcheva I, Nordberg A, Lannfelt L, Långström B, Kilander L. In vivo amyloid imaging with PET in frontotemporal dementia. *Eur J Nucl Med Mol Imaging* 2008; **35**: 100–6.
114 Lucignani G. Clinical applications of PET amyloid imaging: an update. *Eur J Nucl Med Mol Imaging* 2009; **36**: 1185–90.
115 Johnson KA, Gregas M, Becker JA, Kinnecom C, Salat DH, Moran EK, Smith EE, Rosand J, Rentz DM, Klunk WE, Mathis CA, Price JC, Dekosky ST, Fischman AJ, Greenberg SM. Imaging of amyloid burden and distribution in cerebral amyloid angiopathy. *Ann Neurol* 2007; **62**: 229–34.
116 Smid LM, Vovko TD, Popovic M, Petric A, Kepe V, Barrio JR, Vidmar G, Bresjanac M. The 2,6-disubstituted naphthalene derivative FDDNP labeling reliably predicts Congo red birefringence of protein deposits in brain sections of selected human neurodegenerative diseases. *Brain Pathol* 2006; **16**: 124–30.
117 Klunk WE, Mathis CA. The future of amyloid-beta imaging: a tale of radionuclides and tracer proliferation. *Current Opin Neurol* 2008; **21**: 683–87.
118 Agdeppa ED, Kepe V, Petri A, Satyamurthy N, Liu J, Huang SC, Small GW, Cole GM, Barrio JR. In vitro detection of (S)-naproxen and ibuprofen binding to plaques in the Alzheimer's brain using the positron emission tomography molecular imaging probe 2-(1-[6-[(2-[(18)F]fluoroethyl)-(methyl)amino]-2-naphthyl]ethylidene)malononitrile. *Neuroscience* 2003; **117**: 723–30.
119 Rabinovici GD, Furst AJ, O'Neil JP, Racine CA, Mormino EC, Baker SL, Chetty S, Patel P, Pagliaro TA, Klunk WE, Mathis CA, Rosen HJ, Miller BL, Jagust WJ. 11C-PIB PET imaging in Alzheimer disease and frontotemporal lobar degeneration. *Neurology* 2007; **68**: 1205–12.
120 Tolboom N, Yaqub M, van der Flier WM, Boellaard R, Luurtsema G, Windhorst AD, Barkhof F, Scheltens P, Lammertsma AA, van Berckel BN. Detection of Alzheimer pathology in vivo using both 11C-PIB and 18F-FDDNP PET. *J Nuclear Med* 2009; **50**: 191–97.
121 Ikonomovic MD, Klunk WE, Abrahamson EE, Mathis CA, Price JC, Tsopelas ND, Lopresti BJ, Ziolko S, Bi W, Paljug WR, Debnath ML, Hope CE, Isanski BA, Hamilton RL, DeKosky ST. Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. *Brain* 2008; **131**: 1630–45.
122 Bacskai BJ, Frosch MP, Freeman SH, Raymond SB, Augustinack JC, Johnson KA, Irizarry MC, Klunk WE, Mathis CA, Dekosky ST, Greenberg SM, Hyman BT, Growdon JH. Molecular imaging with Pittsburgh Compound B confirmed at autopsy: a case report. *Arch Neurol* 2007; **64**: 431–34.
123 Nelissen N, Van Laere K, Thurfjell L, Owenius R, Vandenbulcke M, Koole M, Bormans G, Brooks DJ, Vandenberghe R. Phase 1 study of the Pittsburgh compound B derivative 18F-flutemetamol in healthy volunteers and patients with probable Alzheimer disease. *J Nucl Med* 2009; **50**: 1251–59.
124 Vandenberghe R, Van Laere K, Ivanoiu A, Salmon E, Bastin C, Triau E, Hasselbalch S, Law I, Andersen A, Korner A, Minthon L, Garraux G, Nelissen N, Bormans G, Buckley C, Owenius R, Thurfjell L, Farrar G, Brooks DJ. 18F-flutemetamol amyloid imaging in Alzheimer disease and mild cognitive impairment: a phase 2 trial. *Ann Neurol* 2010; **68**: 319–29.
125 Zhang W, Oya S, Kung MP, Hou C, Maier DL, Kung HF. F-18 stilbenes as PET imaging agents for detecting beta-amyloid plaques in the brain. *J Med Chem* 2005; **48**: 5980–88.

https://doi.org/10.1017/S0959259812000160 Published online by Cambridge University Press

126 Fodero-Tavoletti MT, Brockschnieder D, Villemagne VL, Martin L, Connor AR, Thiele A, Berndt M, McLean CA, Krause S, Rowe CC, Masters CL, Dinkelborg L, Dyrks T, Cappai R. In vitro characterization of [(18)F]-florbetaben, an Abeta imaging radiotracer. *Nucl Med Biol* 2012; **39**: 1042–48.

127 Villemagne VL, Ong K, Mulligan RS, Holl G, Pejoska S, Jones G, O'Keefe G, Ackerman U, Tochon-Danguy H, Chan JG, Reininger CB, Fels L, Putz B, Rohde B, Masters CL, Rowe CC. Amyloid imaging with (18)F-florbetaben in Alzheimer disease and other dementias. *J Nucl Med* 2011; **52**: 1210–17.

128 Barthel H, Luthardt J, Becker G, Patt M, Hammerstein E, Hartwig K, Eggers B, Sattler B, Schildan A, Hesse S, Meyer PM, Wolf H, Zimmermann T, Reischl J, Rohde B, Gertz HJ, Reininger C, Sabri O. Individualized quantification of brain beta-amyloid burden: results of a proof of mechanism phase 0 florbetaben PET trial in patients with Alzheimer's disease and healthy controls. *Eur J Nucl Med Mol Imaging* 2011; **38**: 1702–14.

129 Choi SR, Golding G, Zhuang Z, Zhang W, Lim N, Hefti F, Benedum TE, Kilbourn MR, Skovronsky D, Kung HF. Preclinical properties of 18F-AV-45: a PET agent for Abeta plaques in the brain. *J Nucl Med* 2009; **50**: 1887–94.

130 Choi SR, Schneider JA, Bennett DA, Beach TG, Bedell BJ, Zehntner SP, Krautkramer MJ, Kung HF, Skovronsky DM, Hefti F, Clark CM. Correlation of amyloid PET ligand florbetapir F 18 binding with Abeta aggregation and neuritic plaque deposition in postmortem brain tissue. *Alzheimer Dis Assoc Disord* 2012; **26**: 8–16.

131 Fleisher AS, Chen K, Liu X, Roontiva A, Thiyyagura P, Ayutyanont N, Joshi AD, Clark CM, Mintun MA, Pontecorvo MJ, Doraiswamy PM, Johnson KA, Skovronsky DM, Reiman EM. Using positron emission tomography and florbetapir F18 to image cortical amyloid in patients with mild cognitive impairment or dementia due to Alzheimer disease. *Arch Neurol* 2011; **68**: 1404–11.

132 Lister-James J, Pontecorvo MJ, Clark C, Joshi AD, Mintun MA, Zhang W, Lim N, Zhuang Z, Golding G, Choi SR, Benedum TE, Kennedy P, Hefti F, Carpenter AP, Kung HF, Skovronsky DM. Florbetapir f-18: a histopathologically validated Beta-amyloid positron emission tomography imaging agent. *Semin Nucl Med* 2011; **41**: 300–4.

133 Tobias M, Yeh LC, Johnson E. Burden of Alzheimer's disease: population-based estimates and projections for New Zealand, 2006–2031. *Aust NZ J Psychiatry* 2008; **42**: 828–36.

https://doi.org/10.1017/S0959259812000160 Published online by Cambridge University Press