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Amyloid imaging

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ABSTRACT

Molecular neuroimaging techniques such as PET are proving valuable in the early and differential diagnosis of Alzheimer's disease (AD). With the advent of new therapeutic strategies aimed at reducing β-amyloid (Aβ) burden in the brain to potentially prevent or delay functional and irreversible cognitive loss, there is increased interest in developing agents that allow assessment of Aβ burden *in vivo*.

Amyloid imaging with PET has proven useful in the discrimination of dementias, showing significantly higher Aβ burden in the gray matter of AD patients when compared with healthy controls or patients with frontotemporal dementia. ApoE ε4 carriers, independent of diagnosis or disease severity, present with higher Aβ burden than non-ε4 carriers. Amyloid imaging matches histopathological reports in aging and dementia, reflecting the true regional density of Aβ plaques in cortical areas. It also appears to be more sensitive than FDG-PET for the diagnosis of AD.

In healthy older people there is an increasing prevalence of amyloid positive scans with age, rising from 20% in the seventh decade to 60% in the ninth decade. Of people with mild cognitive impairment (MCI), 40–60% present with detectable cortical Aβ deposition. In both groups, Aβ deposition is associated with a higher risk for cognitive decline and dementia due to AD. These observations suggest that Aβ deposition is not part of normal aging, supporting the hypothesis that it occurs well before the onset of symptoms and is likely to represent preclinical AD in asymptomatic persons and prodromal AD in MCI. Further longitudinal observations, coupled with different disease-specific tracers and biomarkers, are required to confirm this hypothesis and further elucidate the precise role of Aβ deposition in the course of AD.

Key words: Alzheimer's disease, Aβ, dementia, brain imaging, positron emission tomography

Introduction: Alzheimer's disease and other dementias

Alzheimer's disease (AD), the most common cause of dementia in the elderly, is an irreversible, progressive neurodegenerative disorder clinically characterized by memory loss, and cognitive and functional decline that leads invariably to death, usually within 7–10 years after diagnosis. The progressive nature of neurodegeneration suggests an age-dependent process that ultimately leads to synaptic failure and neuronal damage in cortical areas of the brain critical for memory and higher mental functions. The increasing age of the population in developed countries suggests that, if unchecked, these disorders will become increasingly prevalent (Masters *et al.*, 2006).

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In the absence of specific biological markers, direct pathological examination of brain tissue is still the only definitive method for establishing a diagnosis of AD. The typical macroscopic picture is gross cortical atrophy, whilst microscopically there is widespread cellular degeneration and diffuse synaptic and neuronal loss, accompanied by reactive gliosis and the presence of the pathological hallmarks of the disease: intracellular neurofibrillary tangles (NFTs) and extracellular amyloid plaques (Masters *et al.*, 2006).

Whilst NFTs are intraneuronal bundles of paired helical filaments mainly composed of the aggregates of an abnormally phosphorylated form of tau protein, neuritic plaques consist of dense extracellular aggregates of β-amyloid (Aβ), surrounded by reactive gliosis and dystrophic neurites (Masters *et al.*, 2006). Aβ is a 4-kDa 39–43 amino acid metalloprotein derived from the proteolytic cleavage of the amyloid precursor protein (APP) by β- and γ-secretases. To date, all available evidence strongly supports the notion that an imbalance

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between the production and removal of Aβ leading to its progressive accumulation is central to the pathogenesis of AD (Villemagne *et al.*, 2006).

Post-mortem studies have shown that the distribution and density of Aβ plaques do not correlate consistently with the degree of cognitive impairment in AD. Conversely, the best physiological correlation has been observed with NFTs and soluble levels of Aβ (Masters *et al.*, 2006). These soluble forms of Aβ, in equilibrium with the insoluble Aβ in plaques, are potentially neurotoxic through a number of possible mechanisms, including oxidative stress, excitotoxicity, energy depletion, toxic oxidative interaction with various metal species, inflammatory response and apoptosis (Villemagne *et al.*, 2006). Nevertheless, the exact toxic mechanism by which Aβ effects synaptic loss and neuronal death is still uncertain (Masters *et al.*, 2006).

Currently, the clinical diagnosis of AD is based on progressive impairment of memory, decline in at least one other cognitive domain affecting the activities of daily living, and the exclusion of other diseases (McKhann *et al.*, 1984). A period of up to five years of prodromal decline in cognition, known as mild cognitive impairment (MCI), usually precedes the formal diagnosis of AD (Petersen, 2007). About 40–60% of carefully characterized subjects with MCI will subsequently progress to meet criteria for AD over a 3–4-year period (Petersen, 2007).

Frontotemporal lobe degeneration (FTLD) and dementia with Lewy bodies (DLB) account for about 20% of dementia cases in post-mortem studies. While there is no Aβ accumulation in FTLD, the majority of DLB cases show extensive cortical Aβ deposition along the characteristic α-synuclein-containing Lewy bodies. Cortical Aβ is not present in cognitively intact Parkinson's disease (PD) patients. It may be present, however, when PD patients develop dementia along with Lewy bodies in the neocortex. These data suggest a central role for Aβ in several types of dementia (Villemagne *et al.*, 2006).

There is currently no cure for AD, but a growing understanding of the molecular mechanisms of Aβ formation, degradation and neurotoxicity is being translated into new imaging and therapeutic approaches (Masters *et al.*, 2006).

Need for disease-specific biomarkers

The clinical diagnosis of AD is typically based on progressive cognitive impairments, whilst excluding other diseases. Clinical diagnosis of sporadic disease is challenging; presenting symptoms are often mild and non-specific and can be attributed to a diverse and overlapping pathology presenting similar phenotypes. Confirmation of an AD diagnosis still relies on autopsy. While clinical criteria, together with current structural neuroimaging techniques (computed tomography (CT) or magnetic resonance imaging (MRI)), are sufficiently sensitive and specific for the diagnosis of AD at the mid- to late stages of the disease, they focus on relatively non-specific features, such as memory and functional activity decline and brain atrophy, which are late features in the course of the disease. The neurodegenerative process usually begins decades before symptoms are evident, making early identification based on structural neuroimaging difficult. This in turn precludes early intervention with disease-modifying medications during the presymptomatic period, which by arresting neuronal loss would presumably achieve the maximum benefits of such therapies (Villemagne *et al.*, 2008a).

Therefore, a change in the diagnostic paradigm is needed, where diagnosis moves away from identification of signs and symptoms of neuronal failure – indicating that central compensatory mechanisms have been exhausted and extensive synaptic and neuronal damage is present – to the non-invasive detection of specific biomarkers for particular traits underlying the pathological process (Clark *et al.*, 2008). Given the complexity and sometimes overlapping characteristics of these disorders, and despite recent advances in molecular neurosciences, it is unlikely that a single biomarker will be able to provide the diagnostic certainty required for the early detection of neurodegenerative diseases like AD; especially for the identification of at-risk individuals before the development of the typical phenotype. Therefore, a multimodality approach combining biochemical and neuroimaging methods is warranted (Shaw *et al.*, 2007).

Valid biomarkers are important as they can be used to identify the risk of developing a disease (antecedent biomarkers), aid in identifying disease (diagnostic biomarkers), assess disease evolution (progression biomarkers) or predict future disease course, including response to therapy (prognostic biomarkers).

While neuropsychological evaluation, cerebrospinal fluid (CSF) assessment of Aβ and tau, and structural and molecular neuroimaging (both ^{18}F-fluorodeoxyglucose (FDG) and amyloid imaging) are all good diagnostic biomarkers for AD, evaluation of the data available to date suggests that amyloid imaging and CSF assessments of Aβ are good antecedent biomarkers at the preclinical and prodromal stages of the disease (Jack *et al.*, 2010).

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Conversely, CSF assessments of tau, structural neuroimaging, FDG and neuropsychological evaluation seem to be excellent biomarkers of disease progression (Jack *et al.*, 2010). A review of the literature shows that quantification of $A\beta_{1-42}$, total tau, and p-tau in CSF, FDG and a long list of assessments of global or regional brain atrophy as well as white matter hyperintensities with MRI, have all been proposed as predictors of conversion to AD (Chang and Silverman, 2004; Smith *et al.*, 2008; Jack *et al.*, 2010). While longitudinal studies will further clarify the role of amyloid imaging in predicting conversion from MCI to AD, one of the most important conclusions to be drawn from these studies evaluating Aβ deposition in the brain is that the likelihood of developing AD in a cognitively unimpaired subject with a negative amyloid imaging scan is extremely low (Villemagne *et al.*, 2011).

The other aspect to be considered is prediction of therapeutic response. Amyloid imaging is an appropriate tool to assess eligibility of adequate candidates for anti-amyloid therapeutic trials, while also monitoring – and potentially predicting – treatment response, thus aiding in reducing sample size and minimizing cost while maximizing outcomes. The results from longitudinal studies support the growing consensus that anti-amyloid therapy may need to be given early in the course of the disease, perhaps even before symptoms appear, to be effective, and that downstream mechanisms may also need to be addressed to successfully prevent the development of AD. Furthermore, the slow rate of Aβ deposition indicates that the time window for altering Aβ accumulation prior to the full manifestation of the clinical phenotype may be very wide (Villemagne *et al.*, 2011).

Table 1. Potential clinical roles for Aβ imaging

- Accurate diagnosis of Alzheimer's disease
- Prognosis of conversion to Alzheimer's disease
- Early diagnosis allowing intervention when minimally impaired
- Investigation of the spatial and temporal pattern of Aβ deposition and its relation to disease progression, cognitive decline and other disease biomarkers
- Subject selection for anti-Aβ trials
- Monitoring the effectiveness of anti-Aβ therapy
- Prediction of response to anti-Aβ therapy

Table 2. Ideal Aβ PET radioligand

- Easily labeled with ^{18}F
- Lipid soluble (crosses blood–brain barrier)
- High affinity and selectivity for Aβ plaques
- Slow dissociation from binding site
- Rapidly cleared from blood
- Not metabolized
- Low non-specific binding
- Provide quantitative and reproducible information about Aβ burden in the brain

Amyloid ligands

Aβ plaques and NFTs are the hallmark brain lesions of AD. These microscopic aggregates are still well beyond the resolution of conventional neuroimaging techniques used for the clinical evaluation of patients with AD. While selective tau imaging is starting to show some promising results (Fodero-Tavoletti *et al.*, 2011), the development of molecular imaging methods for non-invasively assessing Aβ burden in AD is already allowing early diagnosis at presymptomatic stages and more accurate differential diagnosis, as well as evaluation of disease-modifying therapy (Villemagne *et al.*, 2008b). Table 1 indicates the potential clinical roles for Aβ imaging.

Since Aβ is at the center of AD pathogenesis, and given that several pharmacological agents aimed at reducing Aβ levels in the brain are being developed and tested, much effort is focused on generating radiotracers or agents that allow Aβ imaging *in vivo* (Villemagne *et al.*, 2008b). For a radiotracer to be useful as a neuroimaging Aβ probe, a number of key general properties are desirable: it should be a lipophilic molecule that crosses the blood–brain barrier (BBB) and is preferably not metabolized, whilst reversibly binding to Aβ in a specific and selective fashion (Villemagne *et al.*, 2008b). Furthermore, low non-specific binding to white matter is desirable (Table 2). Therapies, especially those targeting irreversible neurodegenerative processes, have a better chance of succeeding if applied early, making early detection of the underlying pathological process so important.

Several compounds have been evaluated as potential Aβ probes. Mathis and colleagues at the University of Pittsburgh developed numerous Congo red and Chrysamine-G derivatives for potential use as *in vivo* Aβ probes, but the ability of these relatively large and acidic compounds to cross the BBB was found to be marginal at best. Eventually, it was a thioflavin T derivative, {N-methyl-[C-11]}2-(4′-methylamino-phenyl)-6-hydroxy-benzothiazole ([C-11]6-OH-BTA-1, also known as "Pittsburgh Compound-B" or ^{11}C-PIB, that showed more favorable binding characteristics to fibrillar Aβ both *in vitro* and *in vivo* (Mathis *et al.*, 2002).

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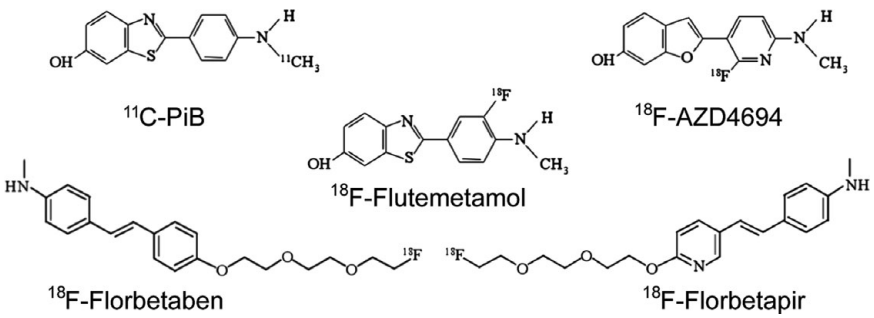


Figure 1. Amyloid ligands. Chemical structure of selected PET amyloid radiotracers that have been used in clinical studies.

While most PET amyloid imaging agents have been shown to display nanomolar affinity for Aβ fibrils, only a few of these agents have found their way into human clinical trials, with studies conducted in AD patients, healthy age-matched controls (HCs) and patients with other dementias using ^{11}C-PiB (Klunk *et al.*, 2004). ^{18}F-Florbetaben (Rowe *et al.*, 2008), ^{18}F-Flutemetamol (Vandenberghe *et al.*, 2010), ^{18}F-Florbetapir (Wong *et al.*, 2010) and ^{18}F-AZD4694 (Jureus *et al.*, 2010) (Figure 1). The different pharmacokinetic and pharmacodynamic characteristics of these radiotracers are discussed in detail elsewhere (Villemagne and Rowe, 2010).

To date, ^{11}C-PiB (Figure 1) has been the most widely used of the currently available amyloid tracers. Unfortunately, the 20-minute radioactive decay half-life of ^{11}C limits its use to centers with an on-site cyclotron and ^{11}C radiochemistry expertise. Consequently, access to ^{11}C-labeled radiotracers is restricted and the high cost of studies is prohibitive for routine clinical use. To overcome these limitations, an Aβ imaging tracer labeled with ^{18}F was required. The 110-minute radioactive decay half-life of ^{18}F permits centralized production and regional distribution as currently practiced worldwide in the supply of FDG for clinical use. There are now several amyloid ligands labeled with ^{18}F under clinical development.

The first reported amyloid imaging tracer, ^{18}F-FDDNP, developed at the University of California, Los Angeles (UCLA) by Barrio and colleagues has been shown to bind both the extracellular Aβ plaques and the intracellular NFTs in AD (Shoghi-Jadid *et al.*, 2002). Direct comparison of ^{18}F-FDDNP with ^{11}C-PIB in human subjects showed a very limited dynamic range of ^{18}F-FDDNP retention between HCs and AD patients (Tolboom *et al.*, 2009).

^{18}F-Florbetaben (also known as ^{18}F-BAY94–9172) (Figure 1), developed by Bayer-Schering Pharma, has been shown to bind avidly to neuritic and diffuse amyloid plaques and to cerebral amyloid angiopathy (CAA). In human studies, ^{18}F-Florbetaben neocortical retention was higher at 90 minutes post injection in AD subjects compared to HCs and FTLD patients (Rowe *et al.*, 2008). Recently completed phase II clinical studies further confirmed these results (Sabri *et al.*, 2010), while a preliminary study showed no pharmacokinetic differences in HCs of different ethnic background (Senda *et al.*, 2010). An ongoing longitudinal study in MCI subjects is helping to establish the usefulness of ^{18}F-Florbetaben PET in predicting progression to AD (Ong *et al.*, 2010). Matching the reported post-mortem distribution of Aβ plaques, ^{18}F-Florbetaben allowed detection of the presence or absence of AD pathology in the brain in subjects from a wide spectrum of neurodegenerative diseases (Villemagne *et al.*, 2010) (Figure 2).

Another fluorinated tracer, ^{18}F-Flutemetamol (also known as ^{18}F-GE067; Figure 1), developed by GE Healthcare, has just completed Phase 2 studies, in which it was demonstrated to distinguish between AD patients and HCs, displaying a similar regional distribution to ^{11}C-PIB (Vandenberghe *et al.*, 2010).

Developed by Hank Kung for Avid Radiopharmaceuticals, ^{18}F-Florbetapir (also known as ^{18}F-AV-45; Figure 1) is an amyloid tracer with rapid reversible binding characteristics (Wong *et al.*, 2010). Several studies have used ^{18}F-Florbetapir. A multicenter Phase 2 study in AD, MCI and HCs showed the ability of ^{18}F-Florbetapir to discriminate between AD and HC (Sperling *et al.*, 2009). ^{18}F-Florbetapir has been adopted as the amyloid tracer for ADNI 2, and is being used in a large number of therapeutic clinical trials around the world. Recent completion of a Phase 3 study demonstrated a 96% agreement with neuropathology in detecting brain Aβ *in vivo* (Clark *et al.*, 2011). ^{18}F-Florbetapir is about to become the first ^{18}F-labeled radiotracer approved by the Food and Drug Administration (FDA) since FDG.

Still in the early phase of development by Astra-Zeneca, human studies with ^{18}F-AZD4694 (Figure 1) has shown low non-specific binding to white matter, suggesting it might be helpful for the

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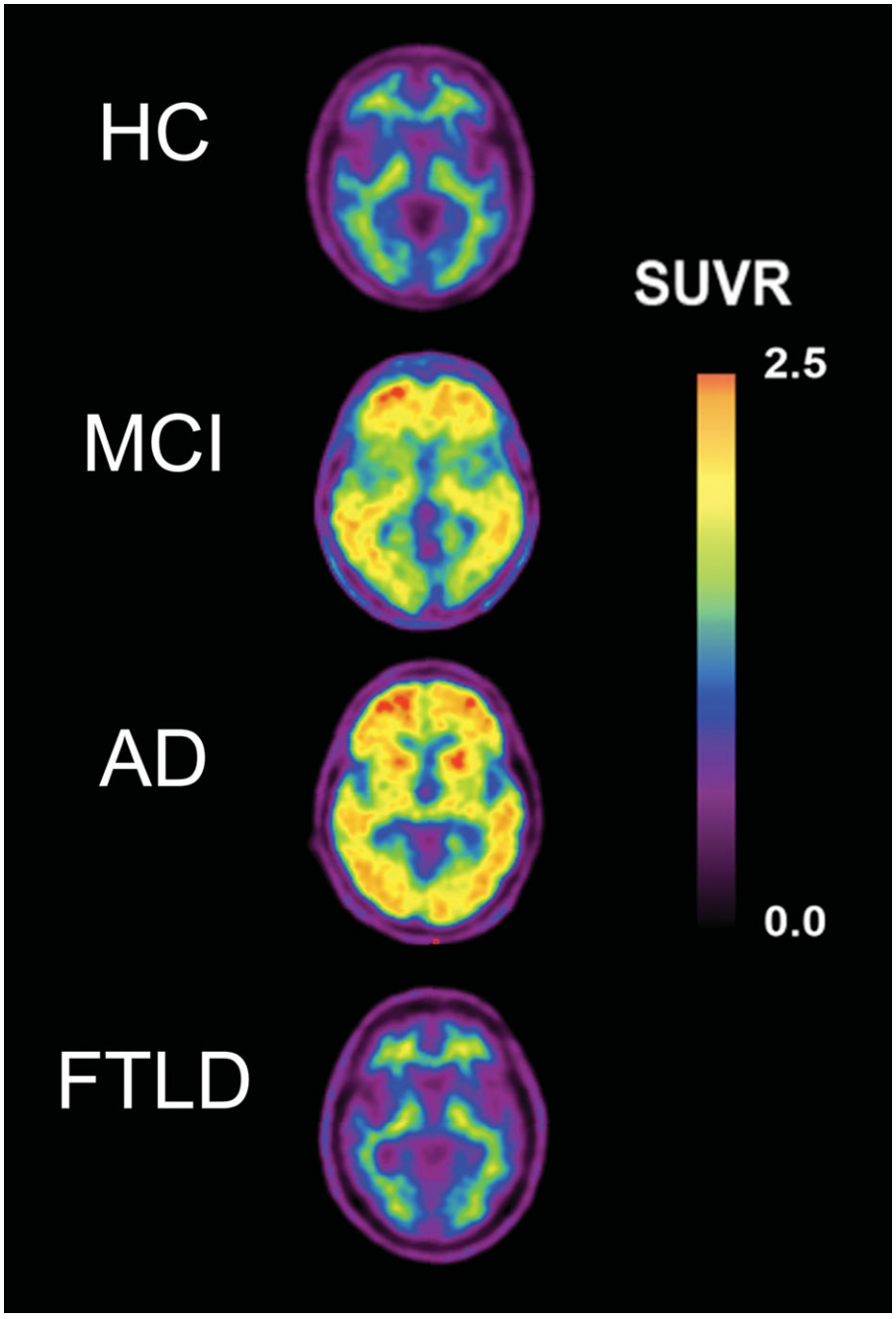


Figure 2. Amyloid imaging with ^{18}F-Florbetaben. Representative transaxial PET images obtained 90–120 minutes post injection of 300 MBq ^{18}F-Florbetaben in a healthy control (HC), a participant classified as mild cognitive impaired (MCI), one subject with Alzheimer's disease (AD) and one with frontotemporal lobar degeneration (FTLD). There is cortical retention of ^{18}F-Florbetaben in the frontal, posterior cingulate/precuneus and lateral temporal areas with relative sparing of occipital and sensori-motor cortex in the MCI and AD subjects. In contrast, there is no cortical ^{18}F-Florbetaben retention in the HC or FTLD subjects. All images are scaled to the same SUVR maximum.

detection of small Aβ cortical deposits at very early stages of the disease process (Jureus *et al.*, 2010).

Amyloid imaging in dementia

Clinical imaging studies with amyloid radiotracers are providing quantitative information on Aβ burden *in vivo*, leading to new insights into Aβ deposition in the brain and facilitating research of neurodegenerative diseases where Aβ may play a role (Masters *et al.*, 2006). Most of the amyloid imaging studies worldwide had been conducted using ^{11}C-PiB.

On visual inspection, cortical retention of ^{11}C-PiB, regardless of disease severity, is markedly elevated in AD (Klunk *et al.*, 2004; Rowe *et al.*, 2007), whilst being generally lower and more

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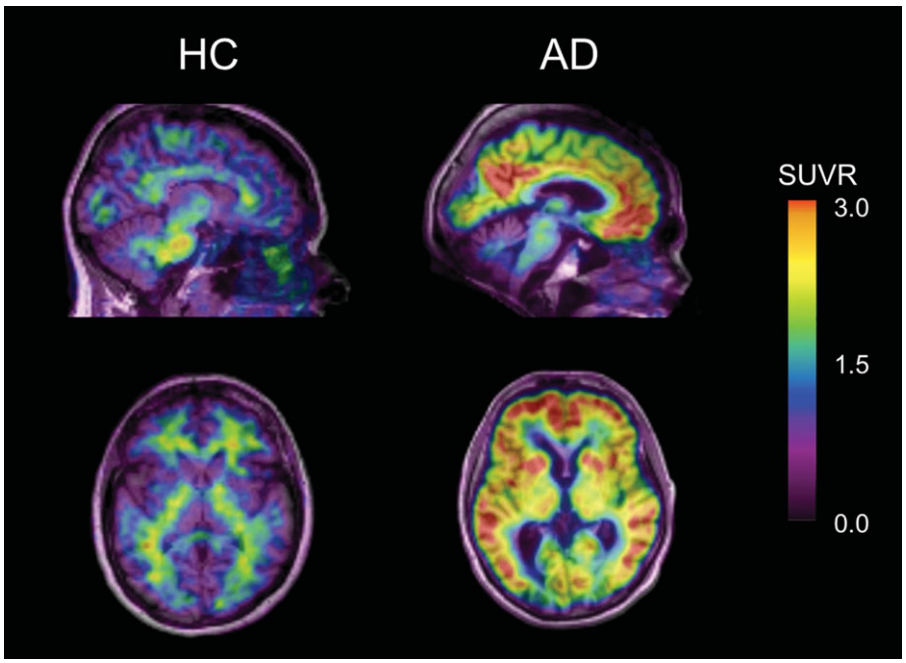


Figure 3. Amyloid imaging with ^{11}C-PiB. Representative 40–70-minute post-injection sagittal and transaxial ^{11}C-PiB PET images overlayed on their respective MRI for a healthy control (HC) subject and an Alzheimer's disease (AD) patient. ^{11}C-PiB PET images show clear differences when comparing cortical ^{11}C-PiB retention in either HC or AD patients. Only non-specific PiB binding in white matter is observed in the HC subject, compared to PiB retention in cortical areas of the AD patient. All images are scaled to the same SUVR maximum.

variable in DLB, probably reflecting a larger spectrum of Aβ deposition (Rowe *et al.*, 2007). In AD, ^{11}C-PiB retention is highest in the frontal, cingulate, precuneus, striatum, parietal and lateral temporal cortex (Figure 3). The occipital cortex, sensori-motor cortex and mesial temporal cortex are usually less affected (Figure 3). With the exception of ^{18}F-FDDNP, which shows high retention in the mesial temporal cortex, a similar pattern of retention in AD is observed with most ^{11}C and ^{18}F amyloid ligands. ^{11}C-PiB binds reversibly, with fastest clearance from the cerebellar cortex and slowest from white matter (Klunk *et al.*, 2004; Rowe *et al.*, 2007). With the exception of familial AD cases (Klunk *et al.*, 2007; Villemagne *et al.*, 2009a) or prion diseases like Creutzfeldt-Jakob disease (Villemagne *et al.*, 2009b), absence of neuritic Aβ plaques in the cerebellar cortex of AD patients is reflected in a similar clearance from this region in all groups (Rowe *et al.*, 2007; Ikonomovic *et al.*, 2008). No significant ^{11}C-PiB cortical retention was observed in a preliminary report on PD patients (Johansson *et al.*, 2008), nor when it was used to discriminate between AD, PD, DLB and PD with dementia (Edison *et al.*, 2008). ^{11}C-PiB-PET has also facilitated differential diagnosis of dementia in patients with atypical onset of dementia who presented with provisional diagnosis of either progressive non-fluent aphasia – considered by many to be a variant of FTLD – or posterior cortical atrophy, respectively (Ng *et al.*, 2007b).

^{11}C-PiB retention is also elevated in subjects diagnosed with CAA (Johnson *et al.*, 2007), and a similar retention pattern is observed in AD and DLB cases (Rowe *et al.*, 2007). There is usually no cortical ^{11}C-PiB retention in patients with clinical diagnosis of FTLD (Rabinovici *et al.*, 2007; Rowe *et al.*, 2007), while analysis of ^{11}C-PiB binding in subjects diagnosed with MCI, a condition that progresses to AD at a rate of approximately 15% per year (Petersen, 2007), has revealed two distinct ^{11}C-PiB retention patterns. About 60% of MCI cases show cortical ^{11}C-PiB binding similar in distribution and sometimes in degree to AD, while the rest exhibit little or no cortical ^{11}C-PiB retention, similar to HC (Pike *et al.*, 2007).

Interestingly, about 25–35% of asymptomatic age-matched HCs present with cortical ^{11}C-PiB retention, predominantly in the prefrontal and posterior cingulate/precuneus regions (Rowe *et al.*, 2007; Aizenstein *et al.*, 2008; Villemagne *et al.*, 2008b). These findings are in agreement with post-mortem reports that about 30% of older individuals without dementia over the age of 75 years have Aβ plaques, with deposits occurring well before the onset of dementia (Morris and Price, 2001). The retention of ^{11}C-PiB in HCs correlates with subtle memory impairment and a greater risk of cognitive decline (Pike *et al.*, 2007; Villemagne *et al.*, 2008b; 2011), likely to represent what has been termed preclinical AD (Morris and Price, 2001) and this group might comprise those who will

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benefit the most from therapies aimed at reducing or eliminating Aβ from the brain before irreversible neuronal or synaptic loss occurs.

Aβ, cognition and other markers of disease

In vivo amyloid imaging is not only helping elucidate the relation between Aβ deposition and cognition but is also allowing researchers to define and refine its relationship with cerebrospinal fluid (CSF) and genetic biomarkers, as well as to establish the relation between Aβ deposition, neuropathology, brain atrophy and glucose metabolism.

^{11}C-PiB PET studies have not only shown a robust difference in ^{11}C-PiB retention between AD patients and HC (Klunk *et al.*, 2004; Rowe *et al.*, 2007), but also inverse correlations with decreased CSF Aβ_{42} (Fagan *et al.*, 2006) and cerebral atrophy (Chetelat *et al.*, 2010). Amyloid imaging data concur both with post-mortem reports on the regional density and sequence of Aβ deposition (Braak and Braak, 1997). The regional retention of ^{11}C-PiB reflects the regional density of Aβ plaques, as reported at autopsy (Ikonomovic *et al.*, 2008), with a higher plaque density in the frontal cortex than in hippocampus, consistent with previous neuropathological and PiB PET reports (Rowe *et al.*, 2007). Recent completion of a Phase 3 study with ^{18}F-Florbetapir demonstrated 96% agreement with neuropathology (Clark *et al.*, 2011). Amyloid imaging also agrees with reports that these neuropathological changes precede the clinical expression of AD by many years, (Morris and Price, 2001) reflected in the large percentage of cognitively unimpaired individuals with significant ^{11}C-PiB retention in the brain (Pike *et al.*, 2007; Aizenstein *et al.*, 2008; Villemagne *et al.*, 2008b). Despite a strong inverse correlation between PiB and FDG in temporal, parietal, and posterior cingulate cortex, the correlation is not present in the frontal lobe or hippocampus (Klunk *et al.*, 2004). Visual assessment of PET images by clinicians blinded to the diagnoses demonstrated that ^{11}C-PiB was more accurate than FDG to distinguish AD from HC (Ng *et al.*, 2007a).

To date, ApoE ε4 is the most consistent genetic risk factor associated with sporadic AD, and its presence is thought to result in an earlier age of onset. Examination of ApoE ε4 allele status revealed that, independent of clinical classification, ε4 carriers present with significantly higher ^{11}C-PiB binding than non-carriers, further emphasizing the crucial role that ApoE plays in the metabolism of Aβ (Reiman *et al.*, 2009; Morris *et al.*, 2010; Rowe *et al.*, 2010). In both symptomatic and asymptomatic adult individuals with mutations within the APP or presenilin 1 genes associated with familial AD, there is high PiB retention in the caudate nuclei, posterior cingulate/precuneus and, to a lesser degree, prefrontal and temporal cortices, retention that seems to be independent of mutation type or disease severity (Klunk *et al.*, 2007; Villemagne *et al.*, 2009a).

To date, the relationship between Aβ deposition and the development of clinical symptoms is not fully understood. Although Aβ burden as assessed by PiB-PET does not correlate with measures of memory impairment in established clinical AD, it does correlate with memory impairment in MCI and healthy older subjects (Pike *et al.*, 2007; Villemagne *et al.*, 2008b). Most subjects classified as non-amnestic single domain MCI do not show significant ^{11}C-PiB retention in the brain, consistent with a non-AD pathological process such as FTLD (Pike *et al.*, 2007; Villemagne *et al.*, 2011). Conversely, 60–80% of amnestic MCI subjects have ^{11}C-PiB retention in the brain (Pike *et al.*, 2007; Villemagne *et al.*, 2011). The observations that PiB retention in individuals without dementia relates to episodic memory impairment, one of the earliest clinical symptoms of AD, suggests that Aβ deposition is not part of normal aging, and supports the hypothesis that Aβ deposition occurs well before the onset of symptoms and is likely to represent preclinical AD. The lack of a strong association between Aβ deposition and measures of cognition, synaptic activity and neurodegeneration in AD, in addition to the evidence of Aβ deposition in a high percentage of MCI subjects and asymptomatic HCs, suggests that Aβ is an early and necessary, though not sufficient, cause for cognitive decline in AD (Villemagne *et al.*, 2008a) and that other downstream mechanisms are involved, likely triggered by Aβ, such as NFT formation, synaptic failure and eventually neuronal loss. Perhaps specific *in vivo* tau imaging will help elucidate or bridge the gap in understanding between Aβ deposition and the persistent decline in cognitive function observed in AD (Fodero-Tavoletti *et al.*, 2011).

Longitudinal studies are helping clarify the relationship between Aβ burden and cognitive trajectory in healthy individuals and MCI subjects. A large longitudinal study with ^{11}C-PiB (Villemagne *et al.*, 2011) showed that Aβ deposition increases slowly in individuals with positive scans whether they have normal cognition, MCI or AD. Furthermore, extensive Aβ deposition was associated with a significantly higher risk of cognitive decline in HCs and with progression from MCI to AD over 1–2 years, denoting the non-benign nature of Aβ deposition. In other reported studies, and probably due to small sample sizes,

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significant increases in PiB retention were found in individuals but not on group analysis (for further discussion see Villemagne *et al.*, 2011). Ongoing large longitudinal studies, including both structural and amyloid neuroimaging studies, as well as genetic and biochemical biomarkers, will permit a better understanding of the role and relevance of Aβ deposition in elderly controls and MCI subjects (Ellis *et al.*, 2009).

Summary

The introduction of radiotracers for the non-invasive *in vivo* quantification of Aβ in the brain has revolutionized the approach to the evaluation of AD. Aβ burden as measured by PET matches histopathological reports of Aβ distribution in aging and dementia, appears more accurate than FDG for the diagnosis of AD, and is an excellent aid in the differential diagnosis of AD from FTLD. ApoE ε4 status is associated with higher Aβ burden. As new therapies enter clinical trials, the role of Aβ imaging *in vivo* is becoming increasingly crucial. Amyloid imaging can provide highly accurate, reliable and reproducible quantitative statements of regional or global Aβ burden in the brain, essential for therapeutic trial recruitment and for the evaluation of disease-specific treatments directed at removing Aβ.

Although Aβ burden as assessed by amyloid agents does not strongly correlate with cognitive impairment in AD, it does correlate with memory impairment and the rate of memory decline in the aging population and MCI subjects. This correlation with memory impairment, one of the earliest symptoms of AD, suggests that Aβ deposition is not part of normal aging, supporting the hypothesis that Aβ deposition occurs well before the onset of symptoms and likely represents preclinical AD. Further longitudinal observations, coupled with different tracers to assess potential downstream effects of Aβ (e.g. selective tau ligands) and biomarkers (e.g. assessment of tau and Aβ in CSF and blood), are required not only to confirm this hypothesis but also to better elucidate the role of Aβ deposition in the course of AD.

Conflict of interest declaration

Dr. Villemagne and Dr. Rowe are consultants for Bayer-Schering Pharma, AG.

Description of authors' roles

Both authors contributed equally to the preparation and writing of this paper.

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References

Aizenstein, H. J. *et al.* (2008). Frequent amyloid deposition without significant cognitive impairment among the elderly. *Archives of Neurology*, 65, 1509–1517.

Braak, H. and Braak, E. (1997). Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiology of Aging*, 18, 351–357.

Chang, C. Y. and Silverman, D. H. (2004). Accuracy of early diagnosis and its impact on the management and course of Alzheimer's disease. *Expert Reviews in Molecular Diagnosis*, 4, 63–69.

Chetelat, G. *et al.* (2010). Relationship between atrophy and beta-amyloid deposition in Alzheimer disease. *Annals of Neurology* 67, 317–324.

Clark, C. M. *et al.* (2008). Biomarkers for early detection of Alzheimer pathology. *Neurosignals*, 16, 11–18.

Clark, C. M. *et al.* (2011). Use of florbetapir-PET for imaging beta-amyloid pathology. *JAMA*, 305, 275–283.

Edison, P. *et al.* (2008). Amyloid load in Parkinson's disease dementia and Lewy body dementia measured with [11C]PIB positron emission tomography. *Journal of Neurology, Neurosurgery and Psychiatry*, 79, 1331–1338.

Ellis, K. A. *et al.* (2009). The Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging: methodology and baseline characteristics of 1112 individuals recruited for a longitudinal study of Alzheimer's disease. *International Psychogeriatrics*, 21, 672–687.

Fagan, A. M. *et al.* (2006). Inverse relation between in vivo amyloid imaging load and cerebrospinal fluid Abeta(42) in humans. *Annals of Neurology*, 59, 512–519.

Fodero-Tavoletti, M. T. *et al.* (2011). [18F]-THK523, a novel in vivo tau imaging ligand for Alzheimer's disease. *Brain*, 134, 1089–1100.

Ikonomovic, M. D. *et al.* (2008). Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. *Brain*, 131, 1630–1645.

Jack, C. R., Jr. *et al.* (2010). Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurology*, 9, 119–128.

Johansson, A. *et al.* (2008). [(11)C]-PIB imaging in patients with Parkinson's disease: preliminary results. *Parkinsonism and Related Disorders*, 14, 345–347.

Johnson, K. A. *et al.* (2007). Imaging of amyloid burden and distribution in cerebral amyloid angiopathy. *Annals of Neurology*, 62, 229–234.

Jureus, A. *et al.* (2010). Characterization of AZD4694, a novel fluorinated Abeta plaque neuroimaging PET radioligand. *Journal of Neurochemistry*, 114, 784–794.

Klunk, W. E. *et al.* (2004). Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Annals of Neurology*, 55, 306–319.

https://doi.org/10.1017/S1041610211000895 Published online by Cambridge University Press

Klunk, W. E. *et al.* (2007). Amyloid deposition begins in the striatum of presenilin-1 mutation carriers from two unrelated pedigrees. *Journal of Neuroscience*, 27, 6174–6184.

Masters, C. L. *et al.* (2006). Molecular mechanisms for Alzheimer's disease: implications for neuroimaging and therapeutics. *Journal of Neurochemistry*, 97, 1700–1725.

Mathis, C. A. *et al.* (2002). A lipophilic thioflavin-T derivative for positron emission tomography (PET) imaging of amyloid in brain. *Bioorganic Medical Chemistry Letters*, 12, 295–298.

McKhann, G. *et al.* (1984). 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*, 34, 939–944.

Morris, J. C. and Price, A. L. (2001). Pathologic correlates of nondemented aging, mild cognitive impairment, and early-stage Alzheimer's disease. *Journal of Molecular Neuroscience*, 17, 101–118.

Morris, J. C. *et al.* (2010). APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. *Annals of Neurology*, 67, 122–131.

Ng, S. *et al.* (2007a). Visual assessment versus quantitative assessment of 11C-PIB PET and 18F-FDG PET for detection of Alzheimer's disease. *Journal of Nuclear Medicine*, 48, 547–552.

Ng, S. Y. *et al.* (2007b). Evaluating atypical dementia syndromes using positron emission tomography with carbon 11 labeled Pittsburgh Compound B. *Archives of Neurology*, 64, 1140–1144.

Ong, K. *et al.* (2010). Assessment of Aβ deposition in mild cognitive impairment with 18F-florbetaben. *Alzheimer's and Dementia*, 6, S26.

Petersen, R. C. (2007). Mild cognitive impairment: current research and clinical implications. *Seminars in Neurology*, 27, 22–31.

Pike, K. E. *et al.* (2007). Beta-amyloid imaging and memory in non-demented individuals: evidence for preclinical Alzheimer's disease. *Brain*, 130, 2837–2844.

Rabinovici, G. D. *et al.* (2007). 11C-PIB PET imaging in Alzheimer disease and frontotemporal lobar degeneration. *Neurology*, 68, 1205–1212.

Reiman, E. M. *et al.* (2009). Fibrillar amyloid-beta burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America*, 106, 6820–6825.

Rowe, C. C. *et al.* (2007). Imaging beta-amyloid burden in aging and dementia. *Neurology*, 68, 1718–1725.

Rowe, C. C. *et al.* (2008). Imaging of amyloid beta in Alzheimer's disease with (18)F-BAY94–9172, a novel PET tracer: proof of mechanism. *Lancet Neurology*, 7, 129–135.

Rowe, C. C. *et al.* (2010). Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. *Neurobiology of Aging*, 31, 1275–1283.

Sabri, O. *et al.* (2010). Florbetaben for beta-amyloid brain PET in Alzheimer's disease: results of a multicenter phase 2 trial. *Alzheimer's and Dementia*, 6, S70.

Senda, M. *et al.* (2010). Inter-ethnic comparability of pharmacokinetics of tlorbetaben (BAY 94–9172), a beta-amyloid imaging PET agent, as a basis of global development of a diagnostics for Alzheimer's disease. *Alzheimer's and Dementia*, 6, S48.

Shaw, L. M. *et al.* (2007). Biomarkers of neurodegeneration for diagnosis and monitoring therapeutics. *Nature Review of Drug Discoveries*, 6, 295–303.

Shoghi-Jadid, K. *et al.* (2002). Localization of neurofibrillary tangles and beta-amyloid plaques in the brains of living patients with Alzheimer disease. *American Journal of Geriatric Psychiatry*, 10, 24–35.

Smith, E. E. *et al.* (2008). Magnetic resonance imaging white matter hyperintensities and brain volume in the prediction of mild cognitive impairment and dementia. *Archives of Neurology*, 65, 94–100.

Sperling, R. *et al.* (2009). PET imaging of beta-amyloid with florpiramine F18 (18F-AV-45): preliminary results from a phase II study of cognitively normal elderly subjects, individuals with mild cognitive impairment, and patients with a clinical diagnosis of Alzheimer's disease. *Alzheimer's and Dementia*, 5, P197 [abstract].

Tolboom, N. *et al.* (2009). Detection of Alzheimer pathology *in vivo* using both 11C-PIB and 18F-FDDNP PET. *Journal of Nuclear Medicine*, 50, 191–197.

Vandenberghe, R. *et al.* (2010). 18F-flutemetamol amyloid imaging in Alzheimer disease and mild cognitive impairment: a phase 2 trial. *Annals of Neurology*, 68, 319–329.

Villemagne, V. L. and Rowe, C. C. (2010). Amyloid ligands for dementia. *PET Clinics*, 5, 33–53.

Villemagne, V. L. *et al.* (2006). The Abeta centric pathway of Alzheimer's disease. In C. J. Barrow and B. J. Small (eds.), *Abeta Peptide and Alzheimer's Disease* (pp. 5–32). London: Springer-Verlag.

Villemagne, V. L. *et al.* (2008a). Abeta deposits in older non-demented individuals with cognitive decline are indicative of preclinical Alzheimer's disease. *Neuropsychologia*, 46, 1688–1697.

Villemagne, V. L. *et al.* (2008b). The ART of loss: Abeta imaging in the evaluation of Alzheimer's disease and other dementias. *Molecular Neurobiology*, 38, 1–15.

Villemagne, V. L. *et al.* (2009a). High striatal amyloid beta-peptide deposition across different autosomal Alzheimer disease mutation types. *Archives of Neurology*, 66, 1537–1544.

Villemagne, V. L. *et al.* (2009b). 11C-PiB PET studies in typical sporadic Creutzfeldt-Jakob disease. *Journal of Neurology, Neurosurgery and Psychiatry*, 80, 998–1001.

Villemagne, V. L. *et al.* (2010). 18F-Florbetaben-PET imaging in the differential diagnosis of dementia. *Alzheimer's and Dementia*, 6, S70–S71.

Villemagne, V. L. *et al.* (2011). Longitudinal assessment of Abeta and cognition in aging and Alzheimer disease. *Annals of Neurology*, 69, 181–192.

Wong, D. F. *et al.* (2010). *In vivo* imaging of amyloid deposition in Alzheimer disease using the radioligand 18F-AV-45 (florbetapir [corrected] F 18). *Journal of Nuclear Medicine*, 51, 913–920.

https://doi.org/10.1017/S1041610211000895 Published online by Cambridge University Press