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REVIEW ARTICLE

A brief history of Aβ imaging

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Abstract

β-Amyloid (Aβ) imaging revolutionized the in vivo assessment of Alzheimer's disease (AD) Aβ pathology and its changes over time, increasing our insights into Aβ deposition in the brain by providing highly accurate, reliable, and reproducible quantitative statements of regional and global Aβ burden in the brain, proving essential for the differential diagnosis, staging, and evaluation of disease-specific anti-Aβ therapeutic approaches. Longitudinal observations, coupled with different disease-specific biomarkers to assess potential downstream effects of Aβ, have confirmed that Aβ deposition in the brain starts decades before the onset of symptoms. Aβ imaging studies continue to refine our understanding of the role of Aβ deposition in AD, and its relation to other imaging and fluid biomarkers.

KEYWORDS
Alzheimer's disease, amyloid, amyloid tracers, aβ imaging, centiloids

Highlights

- Aβ imaging revolutionized the in vivo assessment of Alzheimer's disease Aβ pathology.
- Aβ imaging has increased our insights into Aβ deposition in the brain by providing highly accurate, reliable, and reproducible quantitative statements of regional and global Aβ burden in the brain.
- Aβ imaging is essential for the differential diagnosis, staging, and evaluation of disease-specific anti-Aβ therapeutic approaches.
- Aβ imaging studies continue to refine our understanding of the role of Aβ deposition in Alzheimer's disease, and its relation to other imaging and fluid biomarkers.

1 | INTRODUCTION

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disorder clinically characterized by memory loss and cognitive decline that severely affect the activities of daily living.[1] AD is the leading cause of dementia in the elderly, leading invariably to death, usually within 7–10 years after diagnosis.[2] The progressive nature of the neurodegeneration suggests an age-dependent process that ultimately leads to synaptic failure and neuronal damage in cortical areas of the brain essential for memory and other cognitive domains.[3] AD not only has devastating effects on the sufferers and their caregivers, but it also has a tremendous socioeconomic impact on families and the

health system, a burden which will only increase in the upcoming years as the population of most countries ages.[4] Historically, in the absence of reliable biomarkers, direct pathologic examination of brain tissue derived from either biopsy or autopsy remained the only definitive method for establishing a diagnosis of AD.[5] The pathological hallmarks of the disease: intracellular neurofibrillary tangles (NFT) and extracellular β-amyloid (Aβ) plaques.[6–8] While NFT are intraneuronal bundles of paired helical filaments mainly composed of the aggregates of an abnormally phosphorylated form of tau protein,[9,10] neuritic plaques consist of dense extracellular aggregates of Aβ,[11] surrounded by reactive gliosis and dystrophic neurites. Aβ is a 4 kDa 38–43 amino acid metallopeptide derived from the proteolytic cleavage of the amyloid precursor protein (APP), by β and γ-secretases.[12] To date, most available genetic, pathological, biochemical, and cellular evidence strongly supports the notion that an imbalance between the production and removal of Aβ leading to its progressive accumulation is central to the pathogenesis of AD.[13] The "Aβcentric theory"[1] postulates that Aβ plaque deposition is the primary event in a cascade of effects that lead to neurofibrillary degeneration, synaptic and neuronal loss, and dementia.[14]

Symptomatic treatment with acetylcholinesterase inhibitors or a glutamatergic moderator remains the main provides modest benefit in some patients usually by temporary stabilization rather than a noticeable improvement in memory function.[15] Recently, United States Food and Drug Administration (FDA)-approved antibody therapy administered at the late MCI-early AD stage showed an overwhelming reduction of insoluble Aβ in the brain accompanied by a modest slowing of the rate of disease progression, suggesting or raising hopes that if the same therapy is administered much earlier, before mild objective symptoms of cognitive impairment appear, the onset of the disease could be considerably delayed or even prevented.

Despite the introduction of new diagnostic criteria,[16] clinical diagnosis of AD is still largely based on progressive impairment of memory and decline in at least one other cognitive domain, and by excluding other diseases that might also present with dementia such as frontotemporal lobar degeneration (FTLD), dementia with Lewy bodies (DLB), stroke, brain tumour, normal pressure hydrocephalus, or depression.[17,18] A variable period of up to 5 years of prodromal decline in cognition characterized by a relatively isolated impairment in short-term memory that may also be accompanied by impairments of working memory, known as amnestic mild cognitive impairment (MCI), usually precedes the formal diagnosis of AD.[19,20] A new definition of AD has been proposed based on its underlying pathophysiology instead of a syndromic phenotype, emphasizing the presence of the pathological hallmarks of the disease, that is,Aβ and tau.[21,22] Recently, the classification has been revised and extended to include nonspecific markers of disease, like markers of neuronal failure and neuroinflammation, as well as markers of potential comorbidities such as cerebrovascular disease and α-synuclein proteinopathy.[23] The purpose of this review is to provide a historical perspective of the development and initial use of these Aβ tracers. Their current application and limitations are covered elsewhere.[24]

TABLE 1 Applications of Aβ imaging.

- Accurate and early diagnosis of the underlying pathophysiological process.
- Assessment of the spatial pattern and temporal trajectories and their relation to age, cognitive performance, disease progression, genotype, and other disease biomarkers.
- Validation of new imaging, cognitive and fluid biomarkers
- Disease staging–for example, AT(N)-X framework.
- Early detection allows prognosis and early disease-specific interventions.
- Disease-specific trials:
  - Proof of target engagement
  - Patient selection for disease-specific trials
  - Establish target floor (and ceiling) values for inclusion
  - Predict risk of disease progression/disease staging
  - Establish optimal window for therapeutic intervention
  - Monitor effectiveness
  - Outcome measure

2 | Ab IMAGING RADIOTRACERS

Aβ plaques and NFTs are the pathological 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. Positron emission tomography (PET) is a sensitive molecular imaging technique that allows in vivo quantification of radiotracer concentrations in the picomolar range, allowing the noninvasive assessment of molecular processes at their sites of action, detecting disease processes at asymptomatic stages when there is no evidence of anatomic changes on computed tomography (CT) or magnetic resonance imaging (MRI).[25] Since Aβ is considered 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, and some approved for clinical use, numerous efforts were focused on generating radiotracers for imaging Aβ in vivo.[26–28] Several applications of Aβ imaging have been proposed (Table 1).

As a quantitative neuroimaging probe, the most commonly used Aβ radiotracers have fulfilled several key general properties, like being a lipophilic, nontoxic small molecule with a high specificity and selectivity for Aβ, amenable for high specific activity labeling with ^{18}F or other long lived radioisotope, with no radiolabeled metabolites that enter the brain, while reversibly binding to Aβ.[29–31]

Through the years several compounds have been evaluated as potential Aβ probes: derivatives of histopathological dyes such as Congo red, Chrysamine-G, and Thioflavin S and T,[32–45] nonsteroidal anti-inflammortory drug (NSAID) derivatives,[44,46–49] as well as self-associating Aβ fragments,[50–52] anti-Aβ antibodies or antibodies fragments,[53–55] and serum amyloid P and basic fibroblast growth factor.[56]

Almost a decade after the unsuccessful trials with anti-Aβ antibodies,[53] Aβ imaging came to fruition with the first report of successful imaging in an AD patient with ^{18}F-FDDNP, a tracer that binds both plaques and NFT.[57] Since then, human Aβ imaging PET studies have been conducted in AD patients, normal controls,

and patients with other dementias using ^{11}C-PiB,[58] ^{11}C-SB13,[59] ^{11}C-ST1859,[60] ^{11}C-BF227,[61] ^{11}C-AZD2138[62], ^{18}F-florbetaben[63] ^{18}F-flutemetamol,[64] ^{18}F-florbetapir,[65] and ^{18}F-Flutafuranol—aka NAV4694.[66,67]

While all of the aforementioned radiotracers bind with varying degrees of success to fibrillar Aβ in brain homogenates of AD patients, they do not bind with high affinity to soluble oligomeric forms of Aβ.[68] Some radiolabeled antibodies have been proposed as potential tracers for Aβ oligomers,[69] but we should be aware that Aβ soluble species represent less than 1% of the total Aβ in the brain,[70,71] and remain in a soluble state for about 2-= 4 h before starting fibrillization.[72,73] Until highly selective radiotracers are developed to bind the Aβ soluble species, the contribution of these oligomers to the PET signal in sporadic AD from Aβ tracers such as ^{11}C-PiB or ^{18}F-Florbetaben is considered to be negligible.[74]

2.1 | ^{11}C-labeled radiotracers

2.1.1 | ^{11}C-PiB

^{11}C-Pittsburgh Compound B (PiB) was, and still is in some research institutions with on-site cyclotrons, the most widely used of existing Aβ tracers. PiB has high affinity and selectivity for fibrillar Aβ plaques and other Aβ lesions.[28,75–79] In vitro studies with high specific activity ^{3}H-PiB revealed two distinct binding sites for PiB,[80] and it has been used to assess these binding sites in the frontal cortex and hippocampus.[81] Research has shown that ^{11}C-PiB binds with high affinity to modified forms of Aβ, like the N-terminally truncated and AβN3-pyroglutamate species found in senile plaques.[82] In vitro studies of ^{3}H-PiB binding to white matter homogenates showed no specific binding.[83] PiB, a derivative of Thioflavin T, a dye used to study fibrillization into β-sheet conformation,[84] also binds to other Aβ-containing lesions such as diffuse plaques and cerebral amyloid angiopathy (CAA).[85] PiB shows a much lower affinity for other misfolded proteins with similar β-sheet conformations, such as α-synuclein[86,87] and tau.[85,88] This is important as AD is described as a "triple brain amyloidosis."[89] Most importantly, these studies show that, at a PET scan concentration, ^{11}C-PiB retention in the cortex of individuals with AD or DLB primarily reflects Aβ-related cerebral amyloidosis, rather than binding to Lewy bodies (LB) or NFT.[85,86,88,90] ^{11}C-PiB has consistently provided valuable quantitative data on insoluble Aβ burden in vivo, improving the understanding of Aβ deposition in the brain, allowing earlier detection of AD pathology[58,79,91,92] and facilitating accurate differential diagnoses of dementing neurodegenerative conditions.[91,93,94]

2.1.2 | ^{11}C-BF227

^{11}C-BF-227 (BF227), a benzoxazole derivative, is a promising Aβ imaging tracer.[95] In vitro binding assays with BF-227 revealed a Ki value of 4.3 nM for binding to Aβ1-42 fibrils.[45] A PET study using BF-227 successfully differentiated AD patients from age-matched controls, with AD patients showing significantly higher tracer retention in the cerebral cortex.[61] Regional analysis of the images indicated increased BF-227 retention in the posterior association cortex of AD patients. Unlike PiB, BF-227 exhibits similar binding affinities for both Aβ and α-synuclein.[96]

Several other C-11 Aβ radiotracers have been tested in humans. The stilbene derivative ^{11}C-SB13 was evaluated and found to distinguish between five AD patients and six controls, though it had lower effect size values compared to ^{11}C-PiB.[59] While a preliminary study with the anti-Aβ agent ^{11}C-ST1859 displayed small differences in radiotracer retention between nine AD patients and three healthy controls, it showed that PET can be used to assess the biodistribution and specificity of therapeutic agents.[60] Another Aβ radiotracer, ^{11}C-AZD2138, demonstrated reversible binding and very low nonspecific binding to white matter.[62,97]

2.2 | ^{18}F-labeled radiotracers

The 20-min radioactive decay half-life of carbon-11 restricts the use of ^{11}C-PiB to facilities with an on-site cyclotron and expertise in carbon-11 radiochemistry, making its cost prohibitive for routine clinical use. To address these limitations, several Aβ tracers were labeled with fluorine-18, which has a half-life of 110 min. This allowed for centralized production and regional distribution, which has been developed and tested. ^{18}F-florbetapir,[65,98] ^{18}F-florbetaben,[63,99,100] ^{18}F-flutemetamol,[101,102] and ^{18}F-flutafuranol[67] have successfully replicated the initial results obtained with ^{11}C-PiB.

2.2.1 | ^{18}F-FDDNP

A significant advancement in Aβ imaging tracer development was the synthesis and characterization by Barrio and colleagues of a highly lipophilic radiofluorinated 6-dialkylamino-2-naphthyethylidene derivative (Figure 1), which exhibits nanomolar affinity for Aβ fibrils.[103–105] The tracer, ^{18}F-FDDNP, has been shown to bind both extracellular Aβ plaques and intracellular NFT in AD[57] and to prion plaques in Creutzfeldt–Jakob disease (CJD) brain tissue.[106] However, in vitro studies of FDDNP at concentrations similar to those used in PET scans revealed limited binding to both NFTs and Aβ plaques.[107] ^{18}F-FDDNP—that was used to acquire the first human PET images of Aβ in an 82-year-old woman with AD—showed greater accumulation and slower clearance of ^{18}F-FDDNP in AD patients than controls, particularly in brain areas like the hippocampus.[57] ^{18}F-FDDNP retention in these regions correlated with poorer memory performance, regional glucose hypometabolism, and brain atrophy.[44,49] However, the dynamic range of cortical ^{18}F-FDDNP uptake between healthy controls and AD patients was limited, showing only a 9% difference. Direct comparisons of ^{18}F-FDDNP with ^{11}C-PIB in both monkeys[108] and humans revealed a very limited dynamic range of ^{18}F-FDDNP,[109,110]. Furthermore, in a longitudinal study, ^{18}F-FDDNP proved less useful than ^{11}C-PiB and ^{18}F-fluorodeoxyglucose (FDG) for tracking disease

progression.[111] ^{18}F-FDDNP has also been shown to have brain retention in individuals suspected of chronic traumatic encephalopathy (CTE)[112–114] and primary tauopathies, such as progressive supranuclear palsy (PSP).[115]

2.2.2 | ^{18}F- Flutafuranol

Developed by AstraZeneca, ^{18}F-Flutafuranol (aka NAV4694, AZD4694) shares key characteristics with ^{11}C-AZD2138, including rapid tracer kinetics and minimal nonspecific binding to white matter, similar to ^{11}C-PiB. This makes it useful for detecting small Aβ cortical deposits in the early stages of the disease.[116,117] A head-to-head comparison with PIB suggests ^{18}F-Flutafuranol has a slightly better binding profile than PiB.[67,118] Clinical studies of ^{18}F-Flutafuranol revealed a clear difference in tracer retention between healthy individuals and AD patients[67,118] To date, ^{18}F-Flutafuranol is the only major F-18 Aβ radiotracer that has not been submitted to the FDA for approval.

2.2.3 | ^{18}F-florbetaben

^{18}F-Florbetaben (FBB -aka Neuraceq; AV1; BAY94-9172-) (Figure 1) was the first selective Aβ tracer developed, demonstrating a strong affinity for Aβ in brain homogenates and selectively binding Aβ plaques and CAA in AD tissue sections.[119] At concentrations achieved during human PET studies, FBB did not bind to LB or NFTs in postmortem brain tissue from patients with DLB or FTLD.[120] In clinical studies, cortical retention of ^{18}F-florbetaben was significantly higher at 90 min post-injection in all AD patients compared to age-matched controls and FTLD patients, with binding patterns corresponding to the reported postmortem distribution of Aβ plaques,[63] further confirmed in Phase II clinical studies.[100] A longitudinal study in MCI patients demonstrated that FBB PET is useful for predicting progression to AD.[121,122] FBB correlated highly with PiB,[123,124] and has been used to detect AD pathology in patients across a wide range of neurodegenerative conditions.[99] FBB aided in the differential diagnosis of dementing conditions[125] and helped clarify diagnoses in patients with unclear cerebrospinal fluid (CSF) results.[126] It has been shown that FBB is effective in making accurate antemortem differential diagnoses of Aβ aggregates in the brain[127] confirmed by Phase III studies[128] leading to its approval for clinical use by the FDA.

2.2.4 | ^{18}F-Florbetapir

As FBB, ^{18}F-florbetapir (FBP -aka Amyvid, AV45,—is a stilbene derivative (Figure 1) that was also synthesized by Kung and colleagues at the University of Pennsylvania,[42] and further developed by Avid Radiopharmaceuticals. Initial in vitro studies demonstrated that FBP binds to Aβ plaques in AD brain sections.[129,130] A key feature of this tracer is its rapid reversible binding, which allows scanning just 45—50 min post-injection, similar to PiB.[65] FBP[131] has become the most widely used Aβ radiotracer, and it has been adopted in Alzheimer's Disese Neuroimaging Initiative (ADNI) as designated Aβ radiotracer since ADNI

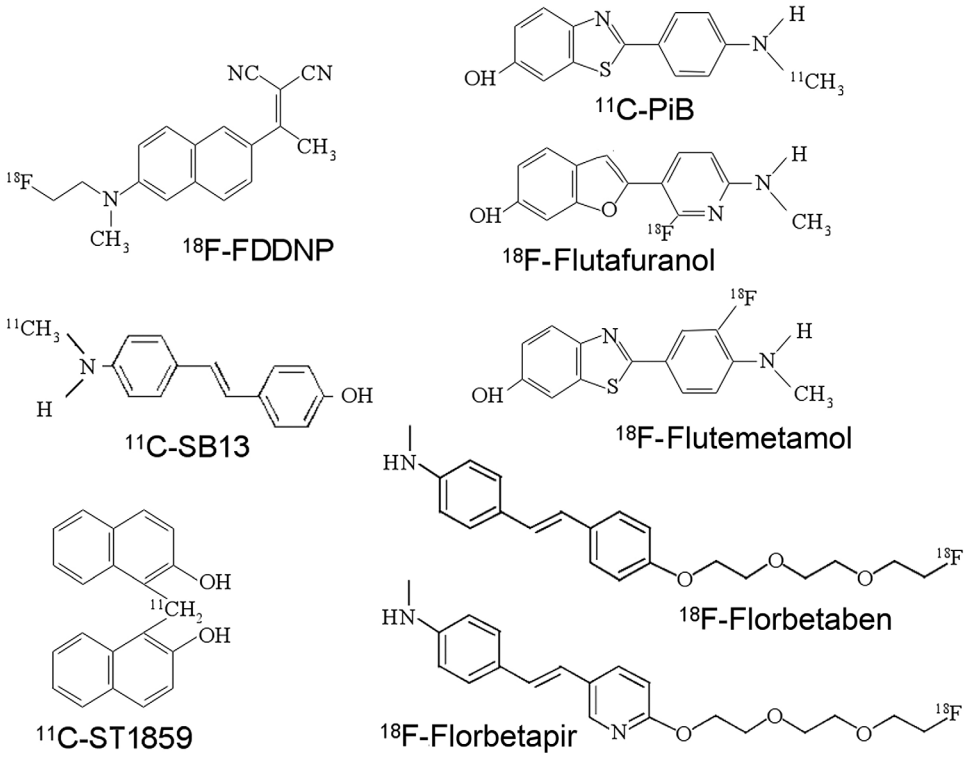

FIGURE 1 Chemical structure of several Aβ radiotracers. Aβ, β-amyloid.

2. It has also been utilized for patient selection and to assess treatment responses in numerous multicenter therapeutic trials worldwide. Several multicenter phase I and II studies in AD, MCI, and healthy controls confirmed FBP's ability to distinguish AD from age-matched controls, with about 50% of MCI patients showing high FBB brain retention.[132] Studies linking Aβ burden and cognition showed that in clinically normal older adults, Aβ burden as assessed by FBP is associated with poorer memory performance.[133] Furthermore, MCI patients with high Aβ burden face a significantly greater risk of cognitive decline over 18 months.[134] An initial Phase III study with 35 volunteers demonstrated a 96% agreement between FBP imaging and neuropathology for detecting Aβ in vivo, with no retention observed in young controls.[98] A subsequent Phase III study with 59 volunteers confirmed that FBP has a sensitivity of 92% and a specificity of 100% for detecting Aβ pathology.[135] Using FBP has been shown to influence patient management[136] and a combined visual inspection and semi-quantitative approach enhances diagnostic accuracy.[137] Longitudinal studies comparing ^{18}F-florbetapir with PiB showed no significant differences in Aβ accumulation rates, but a gradual increase in florbetapir signal was noted in young controls[138] which correlated with early cognitive decline[139,140] even at low Aβ levels.[141] FBP became the first radiotracer approved by the FDA for the in vivo detection of Aβ and the first ^{18}F-labeled radiotracer approved by the FDA since FDG.

2.2.5 | ^{18}F-Flutemetamol

After completion of a Phase III study,[142] ^{18}F-flutemetamol (Flute—aka Vizamyl, GE067), developed by GE Healthcare[64,143] was another fluorinated Aβ tracer (Figure 1) approved by the FDA for clinical use. Phase I and II studies demonstrated that Flute can clearly differentiate between AD patients and healthy controls,[101,102] and that when combined with measures of brain atrophy, it could predict disease progression in participants with MCI.[144] Flute brain retention is highly correlated with both PIB,[101,145,146] and with neuropathology[147–150] where there was no significant difference in Flute's regional brain distribution between MCI and AD participants with end-stage disease.[151] Furthermore, Flute has been shown to assist in the clinical diagnosis and management of individuals experiencing memory decline.[152,153]

2.2.6 | Other ^{18}F tracers

A few other novel ^{18}F-radiotracers, like ^{18}F-FIBT or ^{18}F-FPYBF-2, have been proposed, where clinical proof of concept studies were performed[154–157] but they did not find wide adoption by the research community.

3 | CLINICAL AND RESEARCH APPLICATIONS OF AMYLOD IMAGING

Aβ imaging has been extensively used in both research and various disease-specific therapeutic trials, while also establishing its role as a diagnostic and prognostic tool in the clinical evaluation and management of dementia patients.

3.1 | Aβ imaging in large cohort observational studies

Since the launch of the ADNI in 2003 (https://adni.loni.usc.edu) in the United States, a growing number of similar consortia have been organized and assembled globally, like the Australian Imaging, Biomarker and Lifestyle (AIBL) study of aging (https://aibl.csiro.au),[158] and Europe's Amyloid Imaging to Prevent Alzheimer's Disease (AMYPAD) (http://amypad.eu).[159] These consortia laid out the groundwork and facilitated biomarker discovery and the establishment of standards for the early diagnosis of sporadic AD.[160] A similar worldwide consortium, the Dominantly Inherited Alzheimer's Network (DIAN) (https://dian.wustl.edu),[161] focused on autosomal mutations that inexorably lead to AD. The various achievements of these large cohort observational studies, particularly in the field of Aβ imaging, have significantly advanced our understanding of the underlying pathophysiology of aging and sporadic and familial AD. For example, their observational nature allowed the use of Aβ imaging to establish the natural history of Aβ accumulation in the brain.[162–164] These successes are primarily based on the principles of multimodality, standardization, and data sharing. This multimodal approach has improved our ability to identify individuals with AD-specific traits who are more likely to experience cognitive decline in the near future, making them ideal candidates for smaller, more efficient therapeutic trials. These trials, informed by the shared knowledge of the pathophysiological mechanisms driving aging and AD pathology, can be targeted more, focusing on specific targets or stages of the disease process.

3.2 | Aβ imaging in disease-specific therapeutic trials

Aβ imaging with PET is also contributing to the development of more effective therapies by allowing better selection of patients for multicenter anti-Aβ therapy trials around the world[165] and providing a means to ascertain target engagement and measure their impact on Aβ burden[166–168] as well as outcome measures of their effectiveness.[169–175] Aβ imaging played a central role in the recent FDA approval of three anti-Aβ disease specific monoclonal antibodies.[173–175]

While these studies represent one of the principal applications of Aβ imaging today, a key challenge for these trials is that, besides the sides effects associated with amyloid removal such as oedema and microhemorrhages, reductions in Aβ burden, have not been accompanied with frank improvement or cognitive stabilization or participants, only a moderate delay in the rate of cognitive decline.[169–171] Since study participants were, while mild, symptomatic AD patients, treatments were likely implemented too late in the course of the disease, so trials like A4, and now AHEAD A3, have enrolled cognitively normal elderly indi-

viduals with moderate Aβ, aiming at preventing the cognitive decline expected in this cohort.[176,177]

3.3 | Visual interpretation of Aβ PET scans

All Aβ imaging radiotracers exhibit a similar regional pattern of tracer retention in AD, with the highest retention observed in the frontal, temporal, and posterior cingulate cortices (Figure 2). While the cortical retention of FBP, FBB, and Flute allows for a clear distinction between AD patients and healthy controls, the level of cortical retention with FBP and FBB is lower compared to PiB,[123,178] these tracers show a narrower dynamic range of SUVR values, which results in a relatively higher degree of nonspecific binding to white matter. While the cortical retention of Flute is similar to that of PiB, it exhibits much higher nonspecific retention in white matter.[101] This lower signal-to-noise ratio makes visual interpretation of the images more challenging compared to PiB.[179] In contrast, Flutafuranol provides high-contrast images with relatively low retention in white matter and has shown slightly better performance than PiB.[118] While PiB and Flutafuranol PET images in AD patients usually clearly show high cortical radiotracer retention in excess of that in subjacent white matter, show clear high radiotracer retention in the gray matter, exceeding that in the subjacent white matter, the three FDA-approved ^{18}F tracers frequently show loss of the normal gray–white matter demarcation as the predominant evidence of cortical Aβ deposition.[179]

3.4 | The Centiloid scale

One of the challenges in widely implementing Aβ imaging in therapeutic trials or comparing results across different cohorts and centers is the variability in Aβ tracers. These tracers have different pharmacological and pharmacokinetic properties, leading to results in varying dynamic ranges. Additionally, the use of diverse quantitative methods, differing criteria for selecting internal scaling regions, and contrasting thresholds to differentiate high from low Aβ burden in the brain further complicate comparisons. To address this issue, a standardized approach was developed, known as the Centiloid,[180] which consolidates all Aβ imaging results into a single common semiquantitative scale to improve the clinical and research application of Aβ tracers. All F-18 labeled Aβ radiotracers currently in use have since been cross-calibrated against PiB[118,124,181,182] to enable translation into Centiloids.

Another challenge is defining a threshold of "abnormality." One key issue is the continuous nature of Aβ deposition,[183,184] which makes it difficult to establish a definitive cut-off. While thresholds are inherently arbitrary, adopting one requires evidence that it is both relevant and accurate from a diagnostic and/or prognostic perspective. From a clinical standpoint, a visual binary read can be useful in differentiating individuals with significant Aβ burden in the brain from those with a low Aβ burden. Similar challenges arise in research settings. To avoid being constrained by this dichotomy, some researchers use tertiles,[185,186] or multiple levels,[186] while others propose distinguishing two thresholds for "abnormality." One threshold would be more sensitive, designed to detect the early stages of Aβ deposition, typically in cognitively unimpaired elderly individuals, while the other, a higher threshold, would more specifically correlate with high Aβ neuropathology and the clinical phenotype of dementia.[187] The introduction of the Centiloid scale aimed to address this issue by transforming all Aβ tracers' semiquantitative results into a single, universal scale. However, the idiosyncratic properties of each Aβ tracer remain, meaning some of them may be more or less sensitive or accurate in reflecting similar levels of Aβ burden in the brain. Most studies have used neuropathology to establish Centiloid thresholds. For example, a large multicenter study using *ante mortem* PiB PET and neuropathology data found that a threshold of 12.2 Centiloids could distinguish between plaques and no plaques, while a threshold of 24.4 Centiloids identified intermediate-to-high AD neuropathological changes.[188] Similar neuropathology-based thresholds were determined for other Aβ tracers, such as FBB, with a threshold of 21 Centiloids[189] and FBP, with a threshold of 24 Centiloids.[181] One of the problems of using neuropathology to establish thresholds is that it will depend on the technique used for staining brain tissue, so while Aβ radiotracer bind to fibrillar Aβ, immunohistochemistry will bind to all forms of Aβ that contain the same epitope, irrespective of the Aβ being fibrillar or not, so it will identify "more" Aβ than PET, while other techniques using silver staining like CERAD,[190] will only stain dense neuritic -usually cored- plaques and therefore will identify "less" Aβ than PET. The cross-validation will also depend on the underlying type of Aβ deposits,[191] where Aβ imaging would, for example, underestimate Aβ burden in cases with abundant cotton-wool plaques as usually observed in familial AD cases.[192] Another confounder is the time between the antemortem PET study and autopsy, where the Aβ burden could have substantially changed depending on the time elapsed between the two. Even after the adoption of Centiloids, discussions around optimal Aβ imaging thresholds are ongoing.[141,193–197]

3.5 | Appropriate use criteria and clinical impact of Aβ imaging

Clinical criteria for the appropriate use of Aβ imaging have been established, emphasizing the importance of integrating Aβ imaging with a thorough clinical and cognitive evaluation conducted by a clinician experienced in dementia assessment. This approach aims at ensuring a positive impact on patient management.[198,199] These criteria clearly outline the specific situations in which Aβ imaging should be utilized, such as in patients with persistent or progressive unexplained cognitive impairment, progressive atypical or unclear clinical presentations of dementia, or when dementia onset occurs in individuals aged 65 years or younger.[198,200] The criteria also specify situations where Aβ imaging is inappropriate, including cases of probable AD with a typical age of onset, assessment of dementia severity, asymptomatic individuals or those with unconfirmed cognitive complaints, individuals with a family

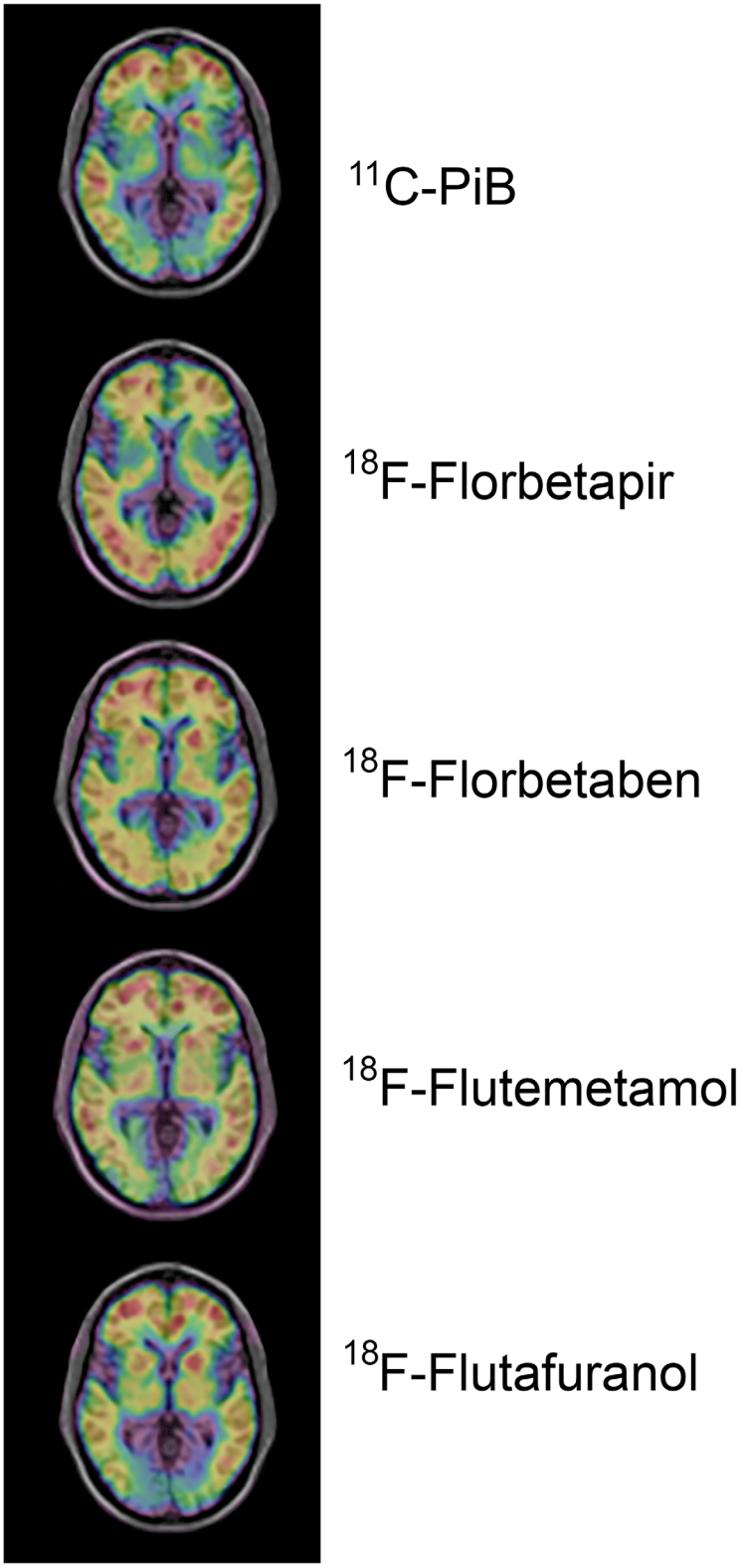

FIGURE 2 Representative transaxial PET images overlaid on MRI from Alzheimer's disease patients obtained with the most commonly used Aβ imaging radiotracers. From top to bottom: ^{11}C-PiB, ^{18}F-florbetapir, ^{18}F-florbetaben, ^{18}F-flutemetamol, and ^{18}F-flutafuranol. Aβ, β-amyloid; MRI, magnetic resonance imaging; PET, positron emission tomography.

history of dementia or carriers the APOE ε4 allele, and nonmedical uses such as for litigation or insurance purposes.[198,200]

These criteria were tested in a multicenter trial, the Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) (https://www.ideas-study.org), assessing the clinical utility of Aβ imaging in the evaluation of patients with MCI or dementia of uncertain origin. The initial findings from this trial indicated that Aβ imaging results led to more than a 60% change in the clinical management of these patients within 90 days. This change was often reflected in an adjustment of their acetylcholinesterase inhibitor medication.[201] Overall, Aβ imaging also

resulted in a change in diagnostic confidence and patient management in up to 60% of cases seen in memory clinics.[201,202]

4 | CONCLUSIONS

The clinical diagnosis of AD is usually made by identifying progressive cognitive decline while excluding other potential conditions. Diagnosing the sporadic form of the disease is particularly difficult, as it often manifests with mild and vague symptoms that can be linked to various overlapping pathologies that share similar characteristics. In general, the accuracy of a clinical diagnosis of AD, compared to neuropathological examination, ranges from 70% to 90%.[203] While clinical criteria, along with current structural neuroimaging techniques (CT or MRI), are sensitive and specific enough for diagnosing AD in its mid to late stages, these methods primarily focus on relatively nonspecific features such as memory loss, functional decline, and brain atrophy, which appear later in the disease's progression. A more effective approach has been suggested in the new diagnostic criteria for AD, proposing a more dynamic model that incorporates biochemical and imaging biomarkers to offer a more accurate predictive framework.[16,204,205] MCI[206] and preclinical AD[207] Aβ imaging allows a more accurate selection of individuals that will benefit from early intervention with anti-Aβ medication, while also providing insights into potential preventive strategies or even new therapeutic approaches.[208,209] In the new diagnostic criteria, dementia is no longer required for the diagnosis of probable AD.[16,21–23,204,205] Thus, as the criteria for the diagnosis of AD change, Aβ imaging is likely, given its impact on patient management,[201] to play an increasingly important role in clinical practice, provided it is accessible and affordable.[210]

While Aβ imaging is still the preferred diagnostic tool to rule out Aβ pathology in individuals being evaluated for cognitive decline, this has been challenged by the recent developments of plasma biomarkers such as plasma Aβ, or p-tau217.[211] Current data clearly indicate that the production and deposition of Aβ is not a harmless process, playing a more significant role during the early, often asymptomatic, stages of AD.[212,213] Therefore, targeting Aβ through anti-Aβ therapy during these early stages appears to be the most promising therapeutic approach.[208] Further, the pathological process of AD typically begins decades before symptoms appear, making early detection challenging. As a result, this delay hinders the opportunity for early intervention with disease-modifying medications during the presymptomatic phase, which, by preventing synaptic and neuronal loss, could potentially offer the greatest benefits of such treatments.[208,214]

Another important consideration is predicting therapeutic response. As new therapies are being implemented, the role of in vivo Aβ imaging is becoming increasingly essential.[215] Aβ imaging serves as an ideal tool for selecting suitable candidates for anti-Aβ therapy, as well as for monitoring and potentially predicting treatment response. Studies have already demonstrated the effectiveness of this technique.[166–168] These findings, combined with results from longitudinal studies, reinforce the increasing consensus that for anti-Aβ therapy to be effective, it may need to be administered early in the disease course, potentially even before symptoms manifest,[208] and that addressing downstream mechanisms will also be necessary to effectively prevent the development of the disease.

The introduction of radiotracers for the noninvasive, in vivo quantification of Aβ burden in the brain has significantly transformed the way AD is evaluated. Aβ imaging enables the in vivo evaluation of brain Aβ pathology and its progression over time, offering highly accurate, reliable, and reproducible quantitative measures of regional or global Aβ burden in the brain. Aβ imaging has provided deeper insights into Aβ deposition, revealing that it occurs long before the onset of symptoms. However, further studies, combined with other novel fluid and neuroimaging biomarkers assessing potential downstream effects of Aβ, are necessary to better understand the role of Aβ deposition in the progression of AD.

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CONFLICT OF INTEREST STATEMENT

Dr. Cohen has nothing to disclose. Dr. Villemagne has been a consultant or paid speaker at sponsored conference sessions for Eli Lilly, Life Molecular Imaging, ACE Barcelona, IXICO, and AC Immune. Author disclosures are available in the Supporting Information.

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SUPPORTING INFORMATION

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

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