PET amyloid imaging across the Alzheimer's disease spectrum: From disease mechanisms to prevention

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Abstract

The advent of amyloid-beta (Aβ) positron emission tomography (PET) imaging has transformed the field of Alzheimer's disease (AD) by enabling the quantification of cortical Aβ accumulation and propagation in vivo. This revolutionary tool has made

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it possible to measure direct associations between Aβ and other AD biomarkers, to identify factors that influence Aβ accumulation and to redefine entry criteria into clinical trials as well as measure drug target engagement. This chapter summarizes the main findings on the associations of Aβ with other biomarkers of disease progression across the AD spectrum. It discusses investigations of the timing at which Aβ pathology starts to accumulate, demonstrates the clinical utility of Aβ PET imaging and discusses some ethical implications. Finally, it presents genetic and potentially modifiable lifestyle factors that might influence Aβ accumulation and therefore be targets for AD prevention.

1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia, a group of brain disorders associated with cognitive decline severe enough to interfere with activities of daily life. While AD is generally known for its devastating effects on one's ability to form and retain memories, the clinical expression of the disease is preceded by a silent phase notably characterized by the pathological accumulation of misfolded amyloid-beta (Aβ) and hyperphosphorylated tau proteins as well as neuronal damage and synaptic failure. The abnormal accumulation of pathogenic proteins was first described well over a century ago. However, it wasn't until the early 1990s that it was suggested that Aβ had a causal role in AD development.[1] This "Amyloid hypothesis" was supported by the observation that single copy mutations in the amyloid precursor protein (APP) and the gamma-secretase pathway (Presenilins) acted as dominant traits provoking an early onset AD phenotype with ~100% penetrance. However, it was challenged by neuropathological findings suggesting that ~30% of cognitively normal older adults have Aβ or tau at autopsy.[2,3] Up until recently, these findings could not be investigated in vivo owing to the absence of a reliable marker of brain Aβ pathology. The introduction of Aβ imaging in the early 2000s has revolutionized AD clinical research. It is now possible to test the amyloid hypothesis using positron emission tomography (PET) imaging of Aβ and longitudinal evaluations of cognitive performance. Over the last two decades the findings resulting from in vivo imaging studies have forced the field to rethink its conception of AD as a clinical entity, helped in differential diagnosis and influenced the clinical management of individuals with neurodegenerative diseases.

In this chapter we discuss the strengths and limitations of molecular imaging as a method for in vivo quantification of Aβ pathology. We summarize the findings of associations between Aβ and other AD biomarkers in the clinical and pre-clinical phases of the disease and how these may have bearing on clinical research and practice. Finally, we discuss the factors that might postpone Aβ appearance, slow down its rate of accumulation and modify its association with other neurodegenerative markers that may be targeted for disease prevention.

2. Molecular imaging of in vivo Aβ pathology

2.1 Amyloid biology

Despite the initial description of senile plaques dating back to Alois Alzheimer's presentation of findings from the first AD patient in 1907, their Aβ component was only elucidated eight decades later.[4,5] The Aβ peptide results from the sequential cleavage of the larger APP protein by β- and γ-secretase. The APP protein is first cleaved by β-secretase and consequently releases a large soluble APP-β fragment. The remaining membrane-bound portion of the protein is then cleaved by γ-secretase. This process is imprecise and thus yields Aβ peptides of varying length of which the most abundant are those ending at amino acid 40 ($A\beta_{40}$) and 42 ($A\beta_{42}$).[6] These Aβ monomers, particularly the $A\beta_{42}$ fragments, can spontaneously aggregate into oligomers, eventually leading to the formation of fibrillar Aβ that makes up senile plaques.[7–9] While senile plaques constitute the main pathological hallmark of the disease, they may only indicate a final, inert, stage of Aβ accumulation since the soluble oligomeric forms are likely those exerting the strongest neurotoxic effects.[10–13]

2.2 Development of Aβ PET tracers and association with other Aβ biomarkers

In the early 2000s, a number of potential probes were investigated for the imaging of Aβ plaques.[14] Derivatives of Congo red and Thioflavin T—two molecules used for staining Aβ plaques in pathology studies—were developed. However, while these probes did bind strongly to Aβ plaques, they failed to effectively cross the blood brain barrier (BBB) thereby resulting in low binding in vivo. Additional efforts to develop antibody-derived tracers were similarly disappointing owing to limited BBB permeability.[14] The first

successful Aβ imaging attempt in humans was achieved using the ^{18}F-FDDNP tracer.[15] Unfortunately, this agent lacked specificity and also bound to neurofibrillary tangles, thus limiting its utility. The AD field had to wait until 2004 for the first clinical study using Pittsburgh Compound B (PiB), a tracer with high affinity and high selectivity for fibrillary Aβ in plaques.[16,17] To date, this remains the most successful and widely used tracer in research settings, often considered as the "gold standard" for imaging of Aβ pathology.[18] However, one of its limitations lies in the use of the ^{11}Carbon radioactive isotope. The relatively short half-life of ^{11}C restricts the clinical utility of this tracer to larger hospitals with a nearby cyclotron. Additionally, and like most Aβ tracers, it shows high affinity mainly for fibrillar Aβ rather than its oligomeric forms.[18–21]

The need for an Aβ tracer that can easily be used in a clinical setting has led to the development and the evaluation of a large number PET or SPECT radiotracers[14] among which three have been approved for clinical use ([^{18}F] Florbetaben, [^{18}F]Florbetapir and [^{18}F]Flutemetamol, Fig. 1).[22] These tracers have the significant advantage over PiB that they are bound to an ^{18}F radioactive isotope which has a longer half-life (~109 mn for ^{18}F vs ~20 mn for ^{11}C). All tracers showed good accuracy for the discrimination of AD patients vs healthy older adults in Phase II and III trials.[23–27] Among newer tracers not yet approved by medical agencies, NAV4694 is a promising ^{18}F tracer which has several appealing features, notably very low unspecific binding in white matter.[28]

Aβ PET tracers were not the first attempts to develop markers to measure Aβ pathology *ante-mortem*. In fact, cerebrospinal fluid measures of Aβ preceded the validation of PiB by more than a decade with the $A\beta_{42}$ fragment being the most sensitive to changes in Aβ accrual.[29,30] Contrary to cortical PET binding, which tends to increase with increasing Aβ plaque deposition in the brain, CSF $A\beta_{42}$ levels decrease progressively with this process. It has been hypothesized that this reduction may result from sequestration of Aβ in plaques at the brain level and is therefore a good proxy of the overall brain Aβ burden.[31]

Aβ-PET presents the distinct advantage over CSF that it provides information on the *quantity* and *extent* of cortical Aβ deposition. Thus, it allows for the study of local interactions between brain Aβ deposition and other disease-related biomarker changes (e.g., brain atrophy, glucose metabolism). While CSF and PET measures of global Aβ deposition are highly correlated, it is possible that they provide distinct information regarding the stage of disease progression.[32–34] Increasing evidence suggests that individuals who are

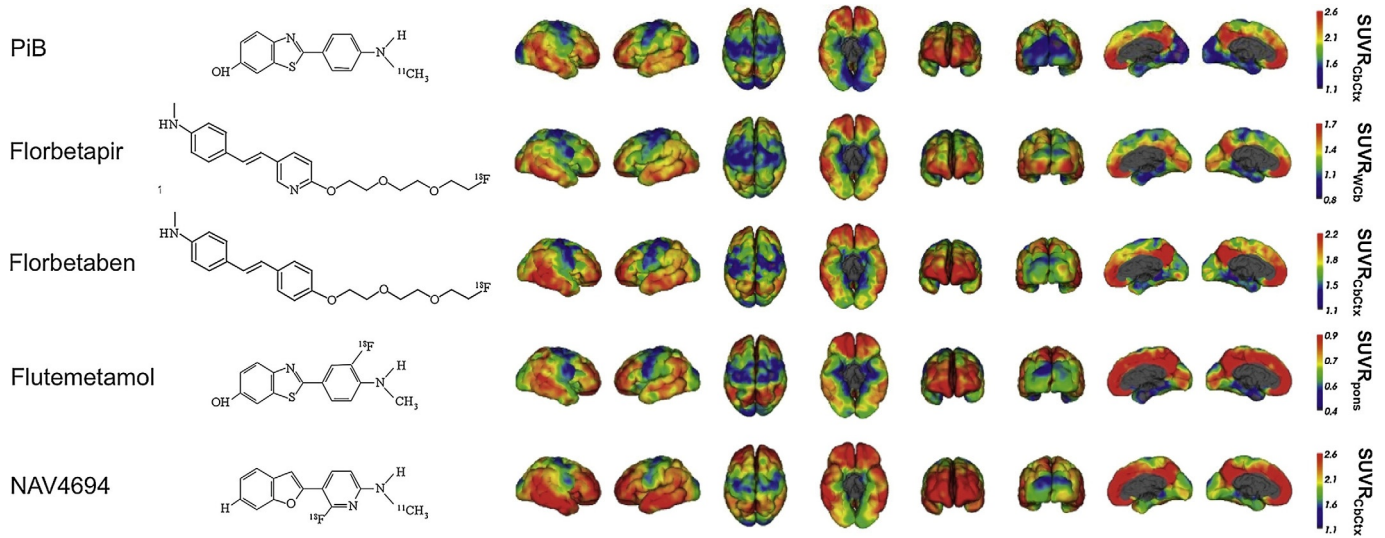

Fig. 1 PET tracers for Aβ imaging. The structure of the first Aβ-specific ligand (PiB), second generation ^{18}F tracers approved for clinical use (Florbetapir, Florbetaben, Flutemetamol) and a third-generation tracer (NAV4694) used for the study of Aβ deposition in humans (left). The stereotypical distribution of Aβ deposition in AD patients is represented for each tracer (right) with high tracer retention in prefrontal, temporal and parietal cortices as well as the cingulate and precuneal areas. *Reproduced with permission from Villemagne VL. Amyloid imaging: past, present and future perspectives.* Ageing Res Rev. *2016;30:95–106.*

positive on CSF Aβ alone (CSF+/PET−) are possibly at an intermediate stage between those who are both negative (CSF−/PET−) or positive (CSF+/PET+) on CSF and PET, although it remains a matter of debate.[35] A study by Palmqvist and colleagues,[34] showed that CSF+/PET− individuals had accruing Aβ PET tracer binding in a restricted set of brain regions thought to be among the first to show Aβ plaques pathology (Fig. 2A). In contrast, CSF+/PET+ persons show widespread accumulation of brain Aβ PET tracer uptake (Fig. 2B). These results suggest that abnormality of CSF Aβ markers may be an earlier event than PET abnormality and thereby allow for earlier detection of AD pathology. Nonetheless, both CSF and PET show similar accuracy for AD diagnosis.[36,37]

More recently, blood tests for the detection of brain Aβ pathology have been developed.[38] The validation of these novel assays uses Aβ PET as a reference to determine Aβ-positivity. These blood tests show good accuracy for the distinction of Aβ PET-negative from -positive individuals and have the advantage of being cheaper and less invasive than PET or CSF collection. Thus, CSF and blood tests for the detection of Aβ pathology may have great potential for future clinical use. Aβ-PET will, however, remain the gold standard to investigate disease mechanisms as it provides information regarding the topography of Aβ lesions.

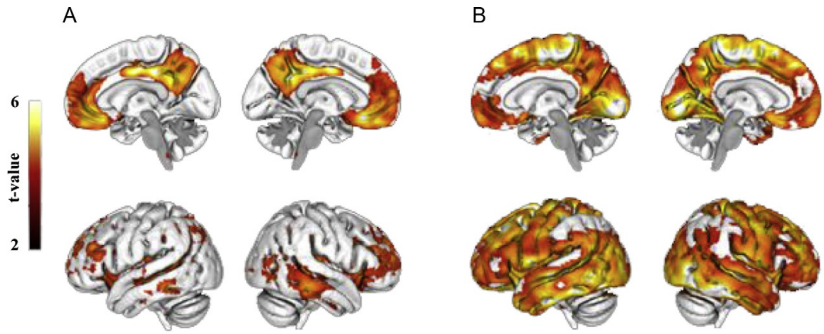

Fig. 2 Aβ accumulation based on CSF/PET status. (A) Individuals showing abnormal CSF Aβ values but subthreshold Aβ PET uptake show increasing PET uptake in medial prefrontal and precuneal regions compared to CSF−/PET− individuals. (B) In contrast CSF+/PET+ participants have a widespread increase in PET binding when compared to CSF−/PET− persons. This suggests that CSF abnormality alone may be an early indicator of the AD pathological process. *Adapted from Palmqvist S, Scholl M, Strandberg O, et al. Earliest accumulation of beta-amyloid occurs within the default-mode network and concurrently affects brain connectivity.* Nat Commun. *2017;8:1214. Springer Nature Limited, CC By 4.0.*

2.3 Aβ-PET quantification and challenges

There is no universal way to quantify cortical Aβ uptake or a widely accepted threshold value to define Aβ positivity, which may be one possible explanation of varying Aβ positivity prevalence across studies, even when they consider older adults in similar age-ranges.[39] It is important to keep in mind that absolute Aβ-PET binding values are extremely difficult to compare across studies because there is substantial differences in PET acquisition parameters, image preprocessing and methods used to define Aβ positivity. While there exists good correlation between different PET Aβ ligands,[40,41] differences in tracer proprieties (e.g., degree and localization of unspecific binding, dynamic range of the tracers) also influence estimations of brain Aβ burden.

Among acquisition parameters that may vary from one study to another, PET scans can be either dynamic or static thereby providing qualitatively different information. While the former corresponds to a full acquisition starting from the time of injection until the tracer activity stabilizes, the latter corresponds to the acquisition when the tracer's activity has reached an equilibrium state. Dynamic scans capture pharmacokinetic and pharmacodynamic properties of the tracer in brain tissue and therefore allow for a truly quantitative measure of tracer uptake.[42] Owing to time constraints, however, static scans are often preferred in clinical and some research settings. Static scan outputs are usually expressed in standardized uptake value ratio (SUVR). SUVRs quantify the amount of tracer uptake using each subject's unspecific binding as its own reference. To do this, a brain region recognized from neuropathology studies as being mainly pathology-free (e.g., cerebellum, white matter) and of having similar biological properties to the regions of interest (e.g., gray matter) is defined as a reference region. The tracer uptake in each brain region of interest is then divided by the uptake in the reference region thereby obtaining an SUVR value theoretically being equal or greater to one. The choice of the optimal reference region for image scaling, however, is subject to debate. The cerebellum has been widely used as reference in cross-sectional studies because it is relatively spared by Aβ accumulation, at least until the most severe stages of amyloidosis. The whole cerebellum is sometimes preferred when using ^{18}F tracers, since they are more prone to high unspecific binding in the white matter.[43] For longitudinal Aβ quantification there seems to be a consensus toward using a white matter reference region rather than a cerebellar one.[44–47] This particular difference may complicate the comparison of results from cross-sectional and longitudinal studies.

Other pre-processing parameters such as the availability of structural magnetic resonance imaging (MRI) scans, correction for partial volume effects, or even the software used for data pre-processing are going to influence PET measures.[47–49] In an effort to improve the comparison of Aβ measurements across pre-processing methods, a working group has proposed a way of standardizing Aβ PET values.[50] The Centiloid project proposes standardized acquisition and pre-processing methods to quantify Aβ PET binding as well as a scaling procedure for PiB and other tracer outputs to a standardized scale. The standardized (or centiloid) scale ranges from 0 to 100, where zero corresponds to values obtained from a group of young individuals and 100 corresponds to values obtained from a group of AD patients. The Centiloid transformation has initially been developed for PiB-PET and has recently been applied to other tracers.[51–54] Using this method, the comparability of multi-site PET scans is improved and may yield common definitions for Aβ positivity.[55,56,56a] Despite these efforts, however, specific tracer kinetics such as the tracer dynamic range may still influence standardized scales and one should always be aware of these.[57]

PET therefore provides a reliable tool to measure Aβ plaque pathology in vivo, but still suffers from a lack of methodological consensus. Despite these difficulties, various Aβ PET tracers and methodologies have been used for imaging of plaque pathology in humans providing important findings which have improved our knowledge of pathological events.

3. Aβ imaging in individuals with cognitive impairment

Dementia refers to a group of syndromes characterized by loss of cognitive functions and inability to perform activities of daily living. In individuals diagnosed with AD dementia, cross-sectional associations between Aβ PET burden, symptoms, and other imaging markers are generally weak. The lack of association of Aβ with other AD biomarkers may owe to the fact that, by the time an individual progresses to the early stages of dementia, the level of cortical Aβ has saturated the neocortex.[58] Nonetheless, in vivo Aβ imaging has enabled the field to recognize the longitudinal dynamics of Aβ accumulation and its associations (or dissociations) with the symptoms and various other biomarkers of AD. Furthermore, Aβ PET used in conjunction with other disease indicators may provide more information about AD progression than Aβ alone. Thus, implementing Aβ PET scan in clinical settings may be an informative tool for patient diagnosis and disease management.

3.1 Associations between Aβ PET and markers of AD progression

Historically, the in vivo diagnosis of AD was based on the nature and the severity of cognitive impairments.[59,60] AD has been classically defined as an amnestic syndrome of the hippocampal type with a signature impairment in episodic memory retrieval that is not rectified by cueing paradigms.[61] In AD, impaired episodic memory can be manifested across a variety of cognitive faculties (free recall, recognition, paired-associate learning) and sensory modalities (auditory, visual, olfactory).[62] AD also affects domains of language ability and semantic knowledge, including object naming, category fluency, semantic categorization, as well as working memory, attention, and visuospatial abilities.[59]

Post mortem assays have shown that the quantity of neurofibrillary tangles, but not Aβ plaques, is correlated with cognitive decline and dementia severity in individuals with AD.[63] Subsequent longitudinal Aβ PET studies have confirmed these findings by demonstrating that the progression of clinical symptoms in late-onset sporadic AD are not coupled with the rate of brain Aβ accumulation,[64] but rather with the rate of neurodegeneration as measured by structural MRI.[65] Other studies have described only weak associations between Aβ PET deposition and late-onset AD dementia symptom severity.[58,66,67] Despite these weak associations, Aβ-positivity is nonetheless associated with an increased risk of conversion to dementia in patients with mild cognitive impairment (MCI).[68] These results might be explained by an observed slowing in rates of Aβ accumulation once symptoms are consistent with a diagnosis of AD dementia.[69] Aβ accumulation is hypothesized to follow a sigmoidal trajectory in which a period of rapid accumulation precedes a quantitative plateau in Aβ deposition, during which dementia symptoms become more severe.[58] This plateau phase may therefore make cross-sectional and longitudinal associations of Aβ with cognition virtually undetectable at this late stage of the disease.

The associations between brain atrophy and Aβ load in AD have also been inconsistent across studies, ranging from absent to showing robust correlations.[70] Assuming that Aβ pathology is no longer a dynamic marker of the disease in the dementia stage,[58] it is possible that observed associations between Aβ and altered brain structural integrity are mediated by associated downstream factors rather than directly caused by Aβ itself. Supporting this idea, the pattern of brain atrophy measured with MRI, or of glucose metabolism measured with Fludeoxyglucose-(FDG) PET does not spatially overlap with brain Aβ deposition.[71,72] Fig. 3 shows AD-related atrophy (orange),

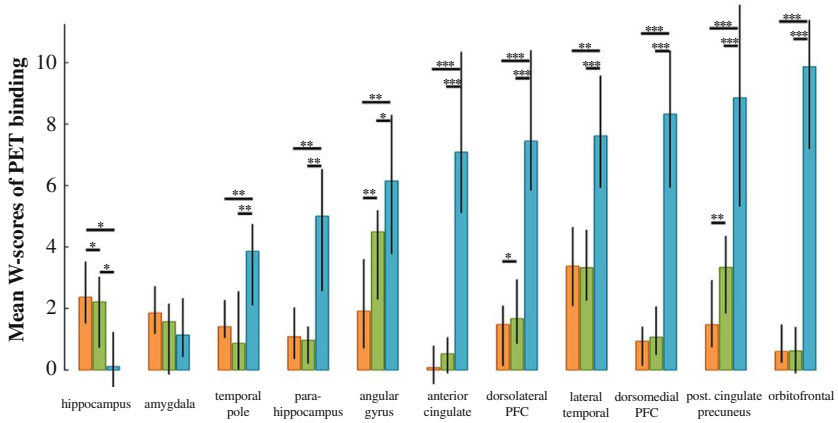

Fig. 3 Aβ deposition pattern does not overlap with atrophy and glucose hypometabolism. The figure shows local degrees of atrophy (orange), hypometabolism (green), and Aβ deposition (blue) expressed as mean W-scores. Increased Aβ deposition does not associate with increased atrophy and glucose hypometabolism. The orbitofrontal cortex for instance has high Aβ deposition but relatively low atrophy and hypometabolism. In contrast, the hippocampus has low Aβ load but nonetheless elevated hypometabolism and atrophy. $^{*}P < 0.05$; $^{**}P < 0.005$; $^{***}P < 0.0001$. Post. cingulate, Posterior cingulate cortex; PFC, prefrontal cortex. *Reprint from La Joie R, Perrotin A, Barre L, et al. Region-specific hierarchy between atrophy, hypometabolism, and beta-amyloid (Abeta) load in Alzheimer's disease dementia.* J Neurosci. *2012;32:16265–16273, with permission.*

hypometabolism (green), and Aβ deposition (blue) in seven brain regions.[72] One striking feature is that very low Aβ-PET binding is found in the hippocampus and the amygdala, two regions with predominant atrophy and hypometabolism. In contrast, very high Aβ-PET binding is found in the orbitofrontal region which almost no atrophy and mainly preserved brain glucose metabolism.

While the patterns of brain atrophy and neuronal failure do not fully overlap with that of brain Aβ deposition, Aβ seems to accumulate in brain regions which are highly functionally connected.[73] Many of the brain regions affected by Aβ in the disease process are members of the default mode network (DMN) and include regions such as the precuneus, medial orbitofrontal cortex, posterior cingulate cortex, anterior cingulate cortex, and angular gyrus.[34,73–75] The DMN comprises a network of functionally connected brain regions that are co-activated during wakeful rest and inhibited during attention-related cognitive tasks. Additionally, episodic memory retrieval is associated with increased activity of regions in the posterior DMN.[76] While the DMN has been the center of interest of

most Aβ-related studies, the Aβ-associated abnormal functional connectivity is not restricted to the DMN[77] and some have therefore argued that the regions expressing strongest Aβ deposition are in fact hubs where multiple networks converge.[70] These hubs could also be the convergence point of multiple pathologies, including tau, the other pathological hallmark of AD.[78,79]

Tau PET imaging is among the most meaningful complementary biomarkers of Aβ PET. Tau radiotracers became available for clinical research in 2012,[80] 8 years after PiB. Much like what is observed for brain atrophy and neuronal death, the topographical pattern and progression of tau deposition is distinct from that of Aβ deposition.[81–84] However, the presence of Aβ seems necessary for tau to spread from the medial temporal lobe to the rest of the neocortex.[85–87] The presence of both proteins is also needed for a definite diagnosis of AD dementia.[88] Thus, using Aβ PET concurrently with tau PET imaging and structural MRI may facilitate the reliable distinction of AD from other diseases in clinical settings.[88] Current tau PET tracers also seem to reliably differentiate topographical patterns between different tauopathies;[89,90] however, they are not presently approved for clinical use.[91]

3.2 Clinical utility and challenges of Aβ PET imaging

3.2.1 *Misdiagnosis and the importance of Aβ imaging in clinical settings*

The advent of Aβ imaging has created several interesting debates regarding the diagnosis criteria of AD. For instance, the diagnosis of probable AD dementia was initially based on the clinical expression of the disease and pathologically confirmed at autopsy. Autopsy studies have suggested that there is a mismatch between clinical and neuropathological diagnoses for up to 30% of individuals diagnosed with dementia.[92] These misdiagnoses include individuals diagnosed as having AD dementia when they have no AD pathology (false positive) and individuals incorrectly diagnosed with another dementia when they have AD pathology (false negative).[93] It is now possible to support the diagnosis of probable AD with Aβ imaging in vivo. PET studies have shown that ~15% of AD-diagnosed individuals have low Aβ tracer binding.[94] These patients usually have a clinical progression of cognitive and behavioral symptoms that are consistent with a neurodegenerative disease, but most of them do not have the AD-typical neurodegenerative profiles suggesting that, at least in some cases, there was a misdiagnosis.[95,96] These misdiagnoses may have important implications for patients. For instance, a NACC-UDS database study showed that 18%–67% of individuals misdiagnosed with AD during their lifetime were

prescribed unnecessary or inappropriate medications.[97] Furthermore, vascular dementia (VD) or Parkinson's disease (PD) patients who were initially misdiagnosed with AD incurred significantly greater annual medical costs (paid to providers through Medicare) than patients who were initially diagnosed correctly.[98] The application of Aβ PET imaging in clinical settings may therefore allow practitioners to make more informed diagnostic decisions since the absence of significant Aβ pathology generally rules out a diagnosis of AD dementia.

3.2.2 Appropriate clinical use

As mentioned above, three Aβ-PET tracers have been FDA-approved for clinical use since 2012: Florbetaben, Florbetapir and Flutemetamol. Florbetapir is currently the most widely used Aβ radiotracer.[99] In 2013, the Amyloid Imaging Taskforce (AIT) developed guidelines to aid clinical translation of Aβ scans.[100] To summarize, according to the AIT's appropriate use criteria, Aβ imaging is appropriate in cases where (a) the patient expresses both subjective and objective cognitive impairment, (b) previous clinical assessment indicated AD as a possible but inconclusive diagnosis, and (c) knowledge of the patient's Aβ status would increase diagnostic certainty and impact patient management. The AIT's examples of appropriate and inappropriate cases are presented in Table 1.

3.2.3 Clinical decision making

Clinical use of Aβ imaging appears to have a significant impact on clinical decision making.[101,102] Across 13 studies on the clinical translation of Aβ imaging conducted between 2012 and 2017, imaging results led to a change in diagnosis in 29% of the cases, an increase in diagnostic confidence in 60% of cases, and prompted an overall change in patient management in 64% of the cases.[101] Additionally, Aβ PET results have a greater impact on practitioners' diagnostic confidence in individuals under 65 years of age, as asymptomatic Aβ deposition is common in older patients and may confound diagnostic accuracy.[100,103]

These results, along with the previously observed rates of misdiagnosis, are in line with the highly anticipated results from the Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study which evaluates the clinical utility and possible benefits for patient health of Aβ scan use in the clinic.[104] IDEAS includes a sample of 11,409 Medicare recipients with MCI or dementia who meet the AIT's appropriate use criteria for Aβ imaging, making it the largest study assessing Aβ imaging in private clinical settings. In this

Table 1 Appropriate use criteria established by the amyloid imaging taskforce.

Appropriate circumstances for Aβ imaging
Patients with persistent or progressive unexplained mild cognitive impairment
Patients satisfying core clinical criteria for possible Alzheimer's disease because of unclear clinical presentation either atypical clinical course or etiologically mixed presentation
Patients with progressive dementia and atypically early age of onset (<65 years or less in age)
Inappropriate circumstances for Aβ imaging
Patients with core clinical criteria for probable Alzheimer's disease with typical age of onset
To determine dementia severity
Solely based on a positive family history of dementia or presence of *APOE* ε4
Patients with a cognitive complaint that is unconfirmed on clinical examination
In lieu of genotyping for suspected autosomal mutation carriers
In asymptomatic individuals
Non-medical usage (e.g., legal, insurance coverage, or employment screening)

Recapitulated from Johnson KA, Minoshima S, Bohnen NI, et al. Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. *Alzheimers Dement.* 2013;9:e-1-16.

cohort, post-PET scan changes in patient management were made for 60.2% of patients with MCI and 63.5% of patients with dementia. Physicians reported that 85.2% of changes in patient management were substantially influenced by Aβ PET results. The most frequent change in patient management was the use of AD drugs. This change is crucial because drugs such as cholinesterase inhibitors and memantine can be prescribed to reduce AD symptoms.[105] However, they are also associated with worse outcomes in frontotemporal dementia and other dementias that don't involve Aβ deposition.[106,107]

The IDEAS team is continuing to collect data on long-term patient outcomes following Aβ-PET-supported diagnoses, which may have implications for whether or not Aβ PET will be eligible for insurance coverage in the future.[108] However, IDEAS does not plan to evaluate the clinical utility of the use of Aβ PET in conjunction with other biomarkers or AD-specific clinical assessments. At present, there is limited research on this

topic.[103] Future investigations will be needed to evaluate whether diagnostic accuracy, confidence, as well as clinical outcomes, could be improved by use of multi-modal assessments. Furthermore, to our knowledge, none of the discussed studies assessing change in patient diagnosis and clinical decision making following Aβ-PET imaging have reported their results stratified by race. Given that recent investigations suggest that (1) African Americans may have a higher incidence of diagnosis of AD dementia compared with non-Hispanic Caucasian Americans[109,110] and (2) African Americans with a dementia diagnosis are more likely to have AD pathology with another mixed neuropathology,[111,112] it would be clinically important to evaluate whether Aβ imaging increases diagnostic confidence proportionately across racial groups. Thus, future investigations should also consider evaluating whether Aβ PET imaging is equally useful and accessible across demographics.

3.2.4 Disclosure of Aβ-PET results for cognitively impaired individuals

There is an ongoing debate about the ethics of Aβ-positivity status disclosure in clinical and research settings. As there is currently no established disease-modifying treatment for AD, valid concerns about patients' psychological well-being in the face of a positive PET scan disclosure have been raised. While this topic is further elaborated upon in a subsequent chapter, it is worth giving a brief overview of Aβ-PET status disclosure.

Ongoing projects, such as the Risk Evaluation and Education of Alzheimer's Disease—the Study of Communicating Amyloid Neuroimaging (REVEAL-SCAN),[113] are studying the behavioral and psychological impacts of revealing Aβ PET scan results in an ethnically diverse cohort of older adults.[113] One such investigation suggested that individuals with MCI who were informed of their Aβ status following a PET scan focused more on the benefits rather than the negative implications of the disclosure.[114] Participants appreciated the opportunity to plan ahead and most individuals also understood that the scan result was not definitive. However, a previous study found that amnestic MCI patients reported both positive and negative outcomes at 2 weeks and 6 months following the disclosure of their Aβ status.[115] All participants with Aβ-positive results reported advantages of the disclosure at both time points, the majority of them also reported perceived disadvantages at 2 weeks, and half of them continued to report disadvantages 6 months later. Here, perceived advantages included enjoying life more, planning, and medication management and perceived disadvantages included increased worry about symptom onset and fear of stigmatization from relatives.

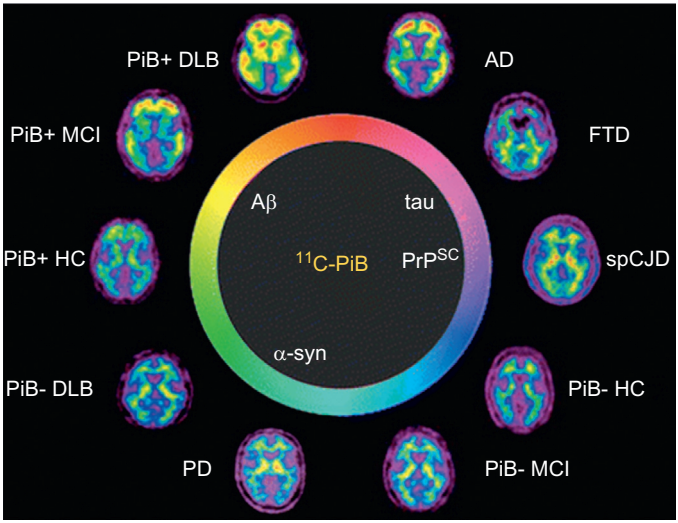

Fig. 4 Aβ positivity is not restricted to AD dementia. Represented are PiB uptake patterns from several Aβ and non-Aβ dementias. Represented clockwise from bottom right corner, Aβ-negative a 73 year-old Aβ-negative control (PiB-HC) subject (MMSE 30), an 83-year-old Aβ-negative subject with mild cognitive impairment (PiB-MCI) (MMSE 28), a 61-year-old Aβ-negative Parkinson's disease (PD) patient (MMSE 27), a 69 year-old Aβ-negative patient with dementia with Lewy Bodies (DLB; MMSE 24), a 77-year-old Aβ-positive healthy control (PiB + HC) subject (MMSE 28), an 82-year-old Aβ-positive subject with mild cognitive impairment (PiB + MCI) (MMSE 28), a 78-year-old Aβ-positive DLB patient (PiB + DLB) (MMSE 19), a 76-year-old Alzheimer's disease (AD) patient (Aβ-positive by definition; MMSE 21), a 59-year-old patient with frontotemporal dementia (FTD; MMSE 20), and a 59-year-old Aβ-positive patient with confirmed sporadic Creutzfeldt-Jakob disease (spCJD). *Reproduced with permission from Fodero-Tavoletti MT, Cappai R, McLean CA, et al. Amyloid imaging in Alzheimer's disease and other dementias.* Brain Imaging Behav. *2009;3:246–261.*

Importantly, a positive Aβ-PET scan alone is not sufficient to rule out other diagnoses or comorbidities. Patients with other age-related neurodegenerative disorders, such as dementia with Lewy bodies (DLB),[116] cerebral Aβ angiopathy,[117] and corticobasal degeneration,[94] also often present with positive Aβ scans (Fig. 4). Nevertheless, as suggested above an Aβ scan could be particularly useful in the evaluation of mildly affected, clinically atypical or early age-at-onset patients.

3.2.5 A β-PET value in disease-modifying interventions

To date, no Aβ-targeting therapy has been approved and the AD field is plagued by large scale failures of these drugs in clinical trials.[118–121] Recent

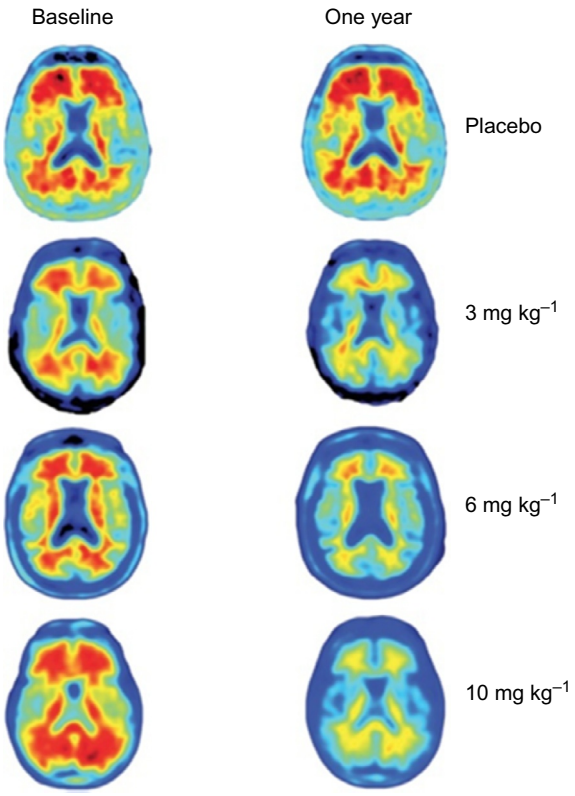

Fig. 5 Use of Aβ PET for evaluation of target engagement. Recent clinical trials have used repeated PET assessments to evaluate whether the drug interacts and clears Aβ deposits. In the phase I trial of the antibody aducanumab, there was an appreciable dose-dependent reduction in Aβ-PET tracer retention after 1 year of treatment. *Reproduced with permission from Sevigny J, Chiao P, Bussiere T, et al. The antibody aducanumab reduces Abeta plaques in Alzheimer's disease.* Nature. *2016;537:50–56.*

compounds have successfully reduced the amount of Aβ in the brain but without slowing of cognitive decline.[122] For example, Fig. 5 shows that the antibody aducanumab successfully decreased fibrillary Aβ deposits as measured with PET in a dose-dependent manner over a 1-year period. However, two phase III trials of this drug were recently terminated following a futility analysis suggesting it would not meet its primary endpoint of reducing cognitive decline in patients with early AD.[123] Many explanations have been brought forward for such treatments' failure to curb cognitive decline, including biochemical properties of the antibodies evaluated and the timing of intervention. However, one important caveat may have been

the lack of systematic evaluation of presence of Aβ pathology in enrolled patients. For example, the failed Bapineuzumab trials enrolled >30% of individuals who were PET Aβ-negative thereby treating patients for a pathology they did not have.[124] One important concern that has arisen from these failed Aβ-targeting trials is whether or not Aβ is a valid target for AD treatment. Also, because Aβ positivity in cognitively normal individuals may be a strong indicator of future AD dementia risk, interventions are now moving even earlier, enrolling patients in the pre-symptomatic stages of disease.

3.3 Conclusions

By the time clinical dementia and AD neuropathology are present, one is already in an advanced stage of AD. At this point in the disease, network dysfunction and brain atrophy are already well underway, and the associations between Aβ and dementia symptoms are difficult to detect. Consequently, this clinical disease stage is probably too late for Aβ-targeting therapy. However, the knowledge of Aβ status appears to be valuable in clinical settings, as it has a measurable influence on physicians' diagnostic and treatment decisions.

4. Aβ imaging in cognitively healthy older adults

It is estimated that Aβ starts to accumulate more than two decades before the onset of dementia.[125–127] One of the most important advances provided by Aβ PET imaging is the visualization of Aβ deposition in the brain of cognitively healthy individuals along with the possibility of longitudinal monitoring of other AD biomarkers, including cognitive status. Over the past ~15 years, several studies have tested the association of Aβ with other markers of brain disease in cognitively normal individuals, both in cross-sectional and longitudinal designs, to better understand early disease mechanisms and identify new prevention strategies.

4.1 Associations of Aβ with other markers of AD progression

Much like what is observed in cognitively impaired patients, the association between brain Aβ deposition and objective measures of cognitive performance in cognitively normal older adults is weakly apparent in cross-sectional studies and, may instead be more related to increasing subjective cognitive decline (i.e., a report of perceived, not objectively measurable, worsening of cognitive abilities).[128] Meta-analyses suggest that, if anything,

there are very subtle associations between increasing Aβ load and worse objective cognitive performance in cognitively normal older adults.[129,130] Associations between baseline Aβ burden and longitudinal cognitive change are less ambiguous and several studies suggest that higher Aβ-PET binding is accompanied by faster subsequent cognitive decline.[69,131–135] This may be particularly evident in people with subjective cognitive decline.[136] However, accelerated cognitive decline in cognitively normal older adults may only become evident after 3–4 years of follow-up,[137] stressing the need for longitudinal research designs that span over decades. People with a positive Aβ-PET scan have also been shown to have an increased risk of converting to dementia.[68,138] Finally, the association of Aβ with decline seems potentiated by evidence of an ongoing neurodegenerative process.[139–142] In this context, neurodegeneration could indicate the presence of a comorbid pathology or a more advanced disease stage.

Similar to what is observed in individuals with dementia, the cross-sectional findings assessing the link between Aβ load and brain damage are inconclusive. For instance, some cross-sectional evaluations suggest that atrophy in a pattern reminiscent of AD is observable in Aβ PET-positive older adults[143,144] while others report no observable atrophy in Aβ positive vs negative persons.[145,146] As is the case for cognitive findings, longitudinal studies provide more consistent evidence of associations between Aβ status and longitudinal brain atrophy.[147–151] This association is also seemingly more apparent for individuals who already have some degree of brain atrophy.[152] In essence, longitudinal brain atrophy would only be accelerated (or apparent) for individuals with evidence of *both* Aβ and neurodegeneration, while it would occur at similar rates for groups of older individuals without either or both Aβ positivity or brain atrophy.[150]

Regarding FDG-PET findings, some reports suggest that global glucose metabolism may increase (i.e., hypermetabolism) in Aβ-positive cognitively normal older adults, possibly reflecting compensation mechanisms.[153,154] Alternatively, it is also possible that high lifelong metabolism drives Aβ deposition.[155] Consistent with this idea, brain regions with the highest Aβ burdens are also those that have high metabolic activity throughout the lifespan.[156] One study of >600 cognitively normal individuals, however, suggested that there exists a modest, negative association of FDG-PET with Aβ-PET in AD-typical regions with aging.[157] These conflicting results may owe in part to the timing in the pathological process at which studies are performed. In the early stages, increased brain metabolic activity may either

be a driver of or a compensatory response to Aβ deposition. At later stages, however, decreased glucose metabolism in the presence of Aβ may reflect early neuronal failure.[158,159]

The timing in the pathological process may also influence findings between Aβ and brain functional connectivity. As previously mentioned, there is a strong overlap between brain Aβ deposition and brain regions that are known to be highly functionally connected.[73] Extensive preclinical work suggests that abnormal neuronal function leads to extracellular release of Aβ[160] and this may modulate the risk of plaque formation.[161] Older adults with childhood-onset epilepsy have, for instance, been found to have increased Aβ burden in late middle age.[162] Increased brain activity throughout the lifespan may therefore facilitate Aβ deposition.[163] Thus, an abnormal increase in neural activity may play an important role in initiating brain Aβ deposition. Similarly to what was proposed for FDG, increased connectivity across different brain networks could also help individuals maintain their cognitive performance while Aβ starts to accumulate.[164,165] Increased Aβ deposition has been associated with greater neural activity in task-positive regions[166,167] and decreased inhibition in task-negative regions (i.e., DMN-like regions) during memory encoding tasks.[168] At later stages, however, Aβ might be related to decreased within-network brain connectivity, possibly reflecting an ongoing neurodegenerative process.[169,170]

Until recently, it was not possible to study the interplay between Aβ and tau in the brain. The combination of Aβ radiotracers with novel tau radioligands now provide an insight on how these two proteins co-occur and interact in vivo. Recent work suggests that Aβ-positivity is accompanied by elevated tau-PET binding in brain regions known to be affected by tau pathology in cognitively normal older adults.[86,87,171] When taken as a continuous variable, global Aβ load is associated with higher regional tau-PET binding even in cognitively unimpaired individuals without clinically significant (i.e., subthreshold) levels of tau pathology.[172] These Aβ-associated elevations in tau-PET binding are especially prevalent in the entorhinal cortex and medial temporal regions, which are among the earliest regions to be affected by *tau* pathology in AD.[173,174]

While the emergence of Aβ pathology may be partly driven by lifelong abnormal neural function or metabolism, the presence of Aβ deposition in older adults relates to future brain atrophy, neuronal failure and cognitive decline.[135,175,176] Longitudinal findings therefore suggest that Aβ accumulation is an early event in the AD pathological process. The limited evidence

of immediate biomarker associations, however, raises the possibility that other actors that coexist with Aβ positivity (e.g., tau) may drive brain and cognitive changes.[177] The future combination of Aβ and tau PET tracers in longitudinal studies will likely improve our appreciation of causal mechanisms.

4.2 Clinical implications

4.2.1 New research clinical criteria

With the availability of Aβ-PET imaging, an increasing amount of research has been devoted to improving the characterization of the preclinical phase of AD. Biomarker-based diagnostic criteria have been proposed by the National Institute on Aging and the Alzheimer's Association (NIA-AA) to identify the disease before the occurrence of the first clinical symptoms.[88] According to the NIA-AA guidelines, these preclinical diagnosis criteria should be restricted to research, their purpose being to accelerate AD-related research discoveries. Aβ-PET imaging has greatly contributed to the conceptual shift of considering AD as a continuum rather than a clinical entity. This framework proposes to classify the disease stage in which a person may be based on the presence or absence of the three pathological hallmarks of AD: Aβ, tau and neurodegeneration. More specifically, this framework suggests that the presence of Aβ is sufficient to be on the AD continuum, while any pathological change in the absence of Aβ-positivity relates to non-AD disease processes. While this biomarker-based definition of AD is not universally accepted, it nevertheless brings a framework to study the changes preceding and probably causing cognitive impairment. Considering AD as a continuum, rather than a chronic disease severe enough to interfere with daily activities, also opens new horizons for preventive interventions.

4.2.2 Disclosure of Aβ-positivity results

The question of disclosure is particularly sensitive in research settings where a proportion of healthy older adults are nonetheless Aβ positive. While cognitively normal individuals would not be eligible for a clinical Aβ-PET scan according to the AIT's appropriate use criteria, they are nevertheless at increased risk of AD dementia. Thus, ethical questions about Aβ-PET disclosure in cognitively normal individuals, bridging the disciplines of psychology, medicine and philosophy, have risen to the forefront of translational AD imaging research.

Clinicians and researchers agree that harm reduction is a guiding principle of biomarker status disclosure. Previous reviews have raised concerns

about the well-being of individuals presented with an early positive Aβ scan, ranging from negative emotions to risk of self-harm. Thus, it has been argued that only patients who meet the AIT's appropriate use criteria should be eligible for AB-PET scan results disclosure.[178] Individuals in early stages of dementia have preserved awareness of their declining cognition and ability to execute planned actions, putting them at potential risk of suicide following a diagnosis of preclinical dementia.[179] Arguably, this severe risk may translate to cases of individuals who present as cognitively normal but are already worried about self-perceived changes in their own cognitive faculties. Suicide is a rare but possible outcome following preclinical disclosure, especially within the first 3 months, and should be taken as a serious outcome risk on a case-by-case basis.[179]

To combat deleterious disclosure-related outcomes rooted in misunderstanding, it is important for individuals to be well informed about what a positive Aβ scan means: while it portends increased risk for AD dementia, it is not a definitive diagnosis and it does not guarantee that one will progress to AD dementia. A recent study assessed healthy older adults' understanding of positive Aβ PET results following disclosure and distribution of informational materials.[180] Among 50 participants, 62% correctly understood that their results indicated a higher risk of progressing to AD dementia and also recognized that there is still a possibility of not developing the disease, although 12% misinterpreted their Aβ status as either an indication of imminent AD onset or equivalent to an AD diagnosis. While comparisons of psychological outcomes between individuals who understood their results and those who didn't were not reported, it is important to ensure that the people understand that a positive scan alone does not equate to a diagnosis or a certain prognosis of AD dementia.

Guidelines about Aβ-PET results disclosure in research settings assessing cognitively normal populations have been drafted in order to minimize harm and maximize participant well-being.[181] Such guidelines recommend accounting for pre-existing psychiatric risk factors when evaluating whether or not results disclosure is appropriate on a case-by-case basis, and also emphasize the importance of education about the meaning of a positive PET scan. Most importantly, clinical researchers should ensure that individuals are informed about psychosocial support resources following disclosure. Despite concerns that Aβ status disclosure among cognitively normal individuals would lead to adverse outcomes, studies assessing responses to disclosure have suggested that positive responses have generally outweighed the negative ones.[182]

4.2.3 Preventive interventions

While Aβ does not seem like an appropriate therapeutic target at the dementia stage, extensive data linking Aβ-positivity to subsequent brain atrophy and cognitive decline suggests that it may be a better target at the earliest stages of the disease. Thus, it is now thought that prevention trials targeting Aβ accumulation have the best chance of success.[183,184] It seems evident that Aβ PET will hold a key role in such trials. For instance, in novel pharmaco-prevention trials such as the A4 study, evidence of Aβ-positivity using either PET or cerebrospinal fluid measures is required for enrollment,[185] and will be necessary to evaluate target engagement. Carefully designed prevention trials, including those in the more predictive autosomal dominant AD, will elucidate *whether* and *when* Aβ can be targeted for prevention.[186] A possibility remains that anti-Aβ therapies may be more efficient even before there is measurable evidence of plaque pathology.

5. "Early" and subthreshold Aβ imaging

5.1 Pitfalls of Aβ-positivity classifications

Most findings discussed thus far emerge from studies that consider Aβ PET as a dichotomous variable, classifying individuals as being Aβ-positive (high binding) vs Aβ-negative (low binding). While this classification simplifies interpretation and is more easily translatable to clinical settings, it also has limitations. As can be seen in Fig. 6, there is not always a clear dichotomy between individuals with (i.e., above the threshold) and without (i.e., below the threshold) Aβ deposition, raising the question of intermediate cases.[74,187] Using a global Aβ index, individuals with "subthreshold" values are thus categorized as Aβ-negative even if most of them probably have some degree of Aβ pathology.[74] Fig. 7, middle row, shows an example of an individual who would be classified as Aβ-negative based on conventional Aβ-PET thresholds but who, nevertheless, shows evidence of moderate Aβ pathology at autopsy according to the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria.

Based on estimated rates of Aβ accumulation,[125] it has been suggested that early increases in PiB-PET signal can be captured about 7 years before an individual reaches a conventional, or conservative, threshold of Aβ positivity.[74] Accordingly, increasing evidence suggests that "subthreshold" individuals accumulate Aβ deposition over time ("Aβ accumulators").[34,188] This "Aβ accumulator" status is additionally associated with memory decline and longitudinal increase in tau-PET binding,[188–190] further suggesting that

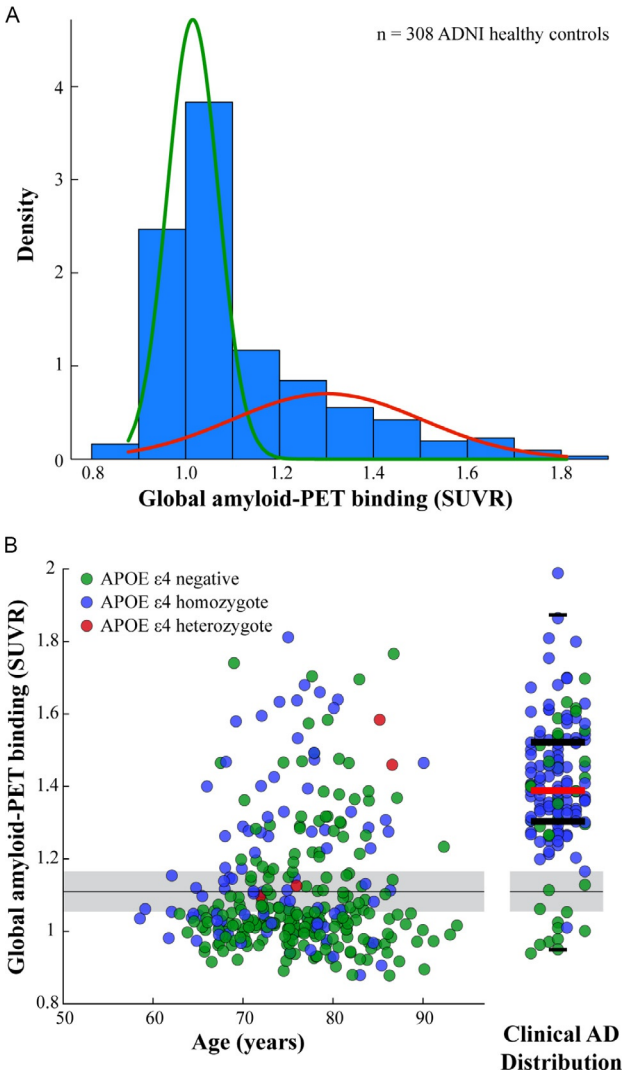

Fig. 6 Characteristic Aβ binding. (A) When plotting the distribution of global cortical Aβ PET tracer retention (SUVR), it often displays a bimodal distribution with a portion of individuals having low binding (usually centered around SUVR = 1.0) and a group with higher binding (here, centered on SUVR = 1.3). Data obtained from Aβ-PET scans (here with AV45) of ADNI participants (http://adni.loni.usc.edu/) who are cognitively healthy. (B) Representation of global cortical Aβ tracer retention as a function of age in ADNI cognitively normal controls (left). The distribution of Aβ tracer binding in clinically diagnosed AD patients is represented on the right. The full black line represents the tracer's Aβ-positivity threshold and gray area highlights a ±5% interval of borderline individuals whose status might change depending on pre-analytical methods or tracer used. The distribution on the right represents the distribution of cortical Aβ binding values in a group of clinically diagnosed AD patients from the ADNI. Clinically diagnosed AD patients with subthreshold Aβ binding may be misdiagnosed and clinicians could reconsider their diagnosis given their negative scan (see Section 3.2.1).

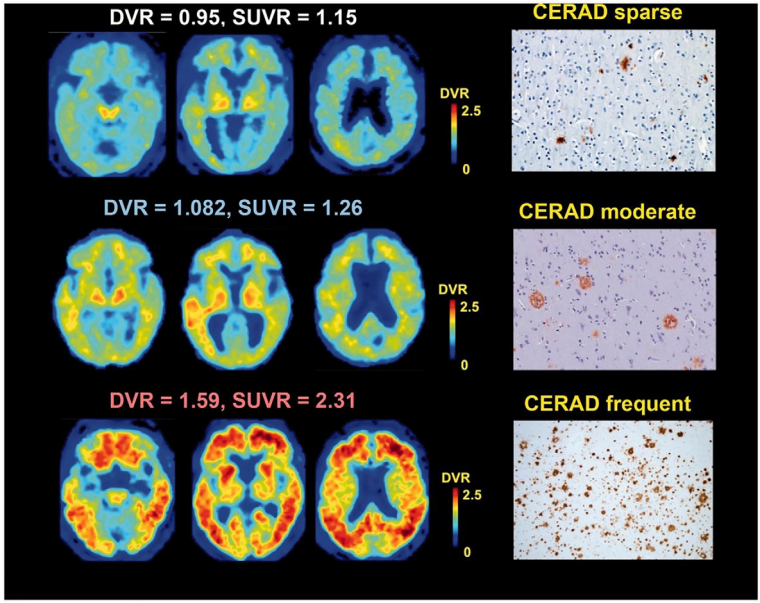

Fig. 7 PiB-PET binding and post-mortem Aβ load. The figure shows trans-axial PiB slices from a patient with CERAD sparse (top row), moderate (middle row) and frequent (bottom row) neuritic plaques. PiB-PET trans-axial slices are presented in neurological orientation. Photomicrographs of Aβ-immunohistochemistry are shown at ×10 (top and bottom rows) or ×20 (middle row) magnification. *Reproduced with permission from Villeneuve S, Rabinovici GD, Cohn-Sheehy BI, et al. Existing Pittsburgh Compound-B positron emission tomography thresholds are too high: statistical and pathological evaluation.* Brain. *2015;138:2020–2033.*

subthreshold levels of Aβ binding are clinically relevant. Considering that (1) Aβ accumulation is supposed to trigger the cascade of brain alterations leading to cognitive decline and AD dementia and (2) it might be more beneficial to stop early Aβ accumulation than to remove it after it has already progressed throughout the cortex, these Aβ-negative individuals at risk of becoming accumulators are probably the most suitable population to target for anti-Aβ prevention trials.

Another disadvantage of classifying individuals as Aβ-positive vs Aβ-negative is that it gets rid of potentially valuable information regarding the spatial distribution of Aβ deposition. Indeed, one key aspect for the early detection of Aβ accumulation may lie in identifying "where" it starts accumulating. While the pattern of tau deposition in AD is described to follow a stereotypical spreading pattern, "ground zero" of Aβ accumulation remains to be determined. Autopsy cases were the first to describe the pattern and

spread of Aβ deposits. While Braak and Braak indicate that spreading might start in the basal neocortex (Stage A),[191] Thal and collaborators found evidence of Aβ deposits throughout the neocortex since the very first stage of beta-amyloidosis.[192] In vivo Aβ-PET imaging enables further investigation of this question. Results have been inconsistent, with some studies reporting that the earliest manifestations of amyloidosis involve the temporal and frontotemporal lobes,[75,193,194] the orbitofrontal-amygdala-hippocampus axes,[195] or more generally throughout the neocortex.[196] The most common assumption, however, is that Aβ deposition starts accumulating in the precuneus and frontal medial regions, often referred to as "AD-signature" regions.[34,74] One hypothesis is that the frontotemporal areas are among the first to show increased Aβ binding,[75,193,194] but this may be a nonspecific process. In contrast, Aβ accumulation in the precuneus and frontal medial regions may be more specific to the AD pathogenetic process and may be more predictive of future Aβ accumulation (Fig. 8).

Alternatively, discrepancies might also indicate that Aβ deposition does not necessarily follow a stereotypical progression and that not all individuals will start accumulating Aβ in the same brain regions.[192] As an example Fig. 9A shows that, in individuals with low (Cluster 1) and high (Cluster 2)

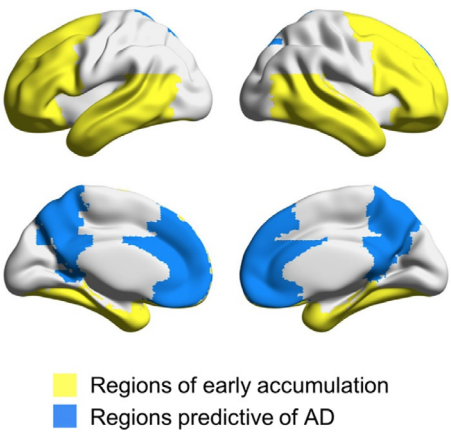

Fig. 8 Preferential regions of Aβ accumulation. Stereotypical patterns of Aβ accumulation when measured using PET. Frontotemporal regions (yellow) may be among the first to show Aβ accumulation but likely represent a process non-specific to AD. In contrast, precuneal and medial frontotemporal regions (blue) are better predictors of future Aβ accumulation and global Aβ burden and are therefore possibly more predictive of an ongoing AD pathological process. *Adapted from Gonneaud J, Arenaza-Urquijo EM, Mezenge F, et al. Increased florbetapir binding in the temporal neocortex from age 20 to 60 years.* Neurology. *2017;89:2438–2446*

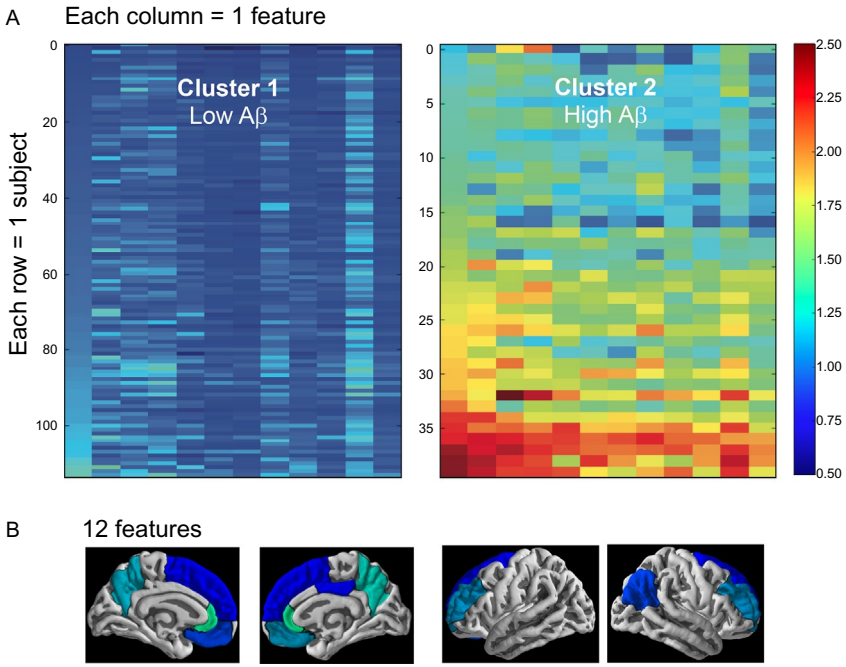

Fig. 9 Non-stereotypical deposition of Aβ. The figure shows the results of a cluster analysis, classifying individuals into two groups based on their Aβ-PET binding values. Panel (A) shows the classification of individuals into low-Aβ (left) or high-Aβ (right) groups as well as intensity of tracer binding (DVR; increasing values indicate more Aβ; color scale ranges from 0.5 to 2.5) in 12 brain regions (features represented in (B) with lighter colors corresponding to the features that have the highest weight in the model). From left to right, the 12 features are: rostral anterior cingulate left hemisphere (lh); rostral anterior cingulate right hemisphere (rh); precuneus rh; precuneus lh; medial orbitofrontal rh; rostral middle frontal lh; rostral middle frontal rh; inferior parietal rh; medial orbitofrontal lh; superior orbitofrontal rh; posterior cingulate rh; and superior orbitofrontal lh. One can notice that, even in the high-Aβ group, the region showing highest tracer uptake may vary from one person to the other, without a stereotypical pattern of tracer distribution. *Reproduced with permission from Villeneuve S, Rabinovici GD, Cohn-Sheehy BI, et al. Existing Pittsburgh Compound-B positron emission tomography thresholds are too high: statistical and pathological evaluation.* Brain. *2015;138:2020–2033.*

Aβ deposition, SUVR values from 12 brain regions (features) which are sensitive to early Aβ PET binding (Fig. 9B) do not follow a stereotypical binding pattern. More particularly, this figure suggests an inter-individual variability in the relative amount of Aβ deposition across key brain regions showing early PET binding in Aβ-positive individuals. For instance, while some individuals (e.g., row 0 of cluster 2) show high PET binging in the

precuneus (column 3 and 4), others (e.g., row 16 of cluster 2) have no binding in this same key region despite the fact that they have high brain Aβ burden. Further studies including longitudinal designs and PET-autopsy comparisons are still needed to elucidate this question.

5.2 How early should we go to detect first evidence of Aβ accumulation?

Related to the question of the earliest regional indicators of Aβ accumulation, some studies have investigated the earliest evidence of Aβ binding throughout the age spectrum of adulthood. Most studies investigating the clinical and prognostic relevance of Aβ-PET have principally focused on late-middle aged adults (~50–60 years of age) even when hypothetical models suggest that Aβ accumulation may occur before that. In fact, considering that some individuals can develop AD dementia before the age of 65 and that Aβ starts accumulating more than two decades before disease onset, some individuals should show evidence of Aβ deposition as early as in their 40s. In line with the objective of identifying individuals at the earliest phase of the pathogenetic process, recent investigations have attempted to identify the youngest age at which Aβ aggregation may start. A handful of studies including individuals <50 years old suggest that Aβ accumulation may start early in adulthood.[75,196–198] This early increase may even be associated with cognitive performance in middle-aged individuals.[197] Although these PET findings were initially surprising, they concurred with some neuropathological studies describing the occurrence of Aβ plaques in individuals—principally *APOE* ε4 carriers—as young as 40 years of age, or even before.[191,199,200]

Thus, Aβ-PET imaging has allowed researchers to gather the first in vivo evidence of the earliest protein accumulation. This has strengthened the need of studying Aβ binding in younger populations and taking advantage of the full information provided by PET scans (i.e., both global and regional Aβ load).

6. Factors influencing amyloid accumulation

The prevalence of Aβ deposition in cognitively normal individuals increases with age, going from ~10% in one's 50s to >30% in individuals over 80 years of age.[68,201] Not all individuals age 80+ have Aβ, however, suggesting that inter-individual differences influence Aβ accumulation.

With the emergence of Aβ imaging, it has been shown that several non-modifiable and potentially modifiable factors can influence Aβ deposition.

6.1 Non-modifiable factors

It was suggested quite early on that "sporadic" AD may have a strong hereditary component.[202,203] Having a first-degree family history (FH) of "sporadic" AD is associated with a 1- to 14-fold increased risk of dementia.[204,205] Accordingly, a family history of AD has been associated with an increased risk of Aβ positivity.[206,207] More recently, our group showed that proximity to one's first-degree relative's age at symptom onset correlates with increased Aβ biomarker load, an association that was stronger in women when compared to men.[208] While these observations may be partly driven by the fact that family history and *APOE* ε4 highly co-occur,[209,210] they may also act synergistically to increase Aβ load.[211]

It is now well established that carriers of the ε4 allele have a 4- to 16-fold increased risk of AD dementia.[212,213] One mechanism by which *APOE* might increase AD risk is via clearance of cerebral Aβ.[214,215] When matched for age, *APOE* ε4 carriers usually have more Aβ deposition than non-carriers.[68,201] Fig. 10 shows an example of two 67-year-old cognitively

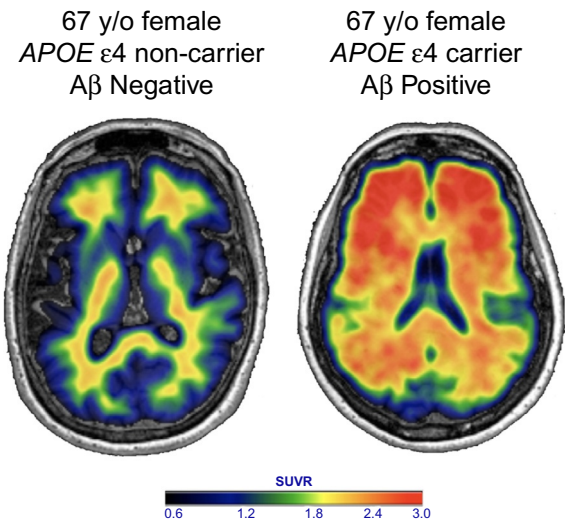

Fig. 10 APOE ε4 and risk of Aβ positivity. Aβ-PET scan of an age and sex matched Aβ-negative APOE ε4 non-carrier (left) and of an Aβ-positive carrier (right) pair from the PREVENT-AD study of cognitively unimpaired older adults at risk of AD.[216]

normal individuals; the one on the left panel is an *APOE* ε4 non-carrier with minimal Aβ-PET binding and the one on the right panel is an *APOE* ε4 carrier with high levels of Aβ-PET binding.

6.2 Modifiable factors

Given the repeated failures of clinical trials involving disease-modifying drugs for AD, a new research field is now investigating modifiable factors that could postpone or slow down Aβ accumulation for disease prevention. Up to 35% of dementia risk is attributable to lifestyle and behavioral factors that are potentially modifiable.[217] Cardiovascular risk factors may be the most recognized among these since higher cardiovascular risk factors in midlife have been associated with increased risk of cognitive decline and dementia.[218–220] More recently, it was suggested that abnormal vascular changes may occur before Aβ abnormality,[221] and that aggressive treatment for hypertension may result in diminished risk of cognitive impairment.[222] The advent of Aβ PET imaging has helped clarify the pathological pathways by which vascular risk factors could influence AD risk. Several studies have shown that midlife cardiovascular risk factors are associated with higher Aβ-PET binding in later life.[223–226] However, these associations were either unobservable or less frequently reported at older ages, suggesting that cardiovascular health earlier in life may have long-term effects on the accrual of AD pathology.[224,226–228]

Cognitive and physical activities have also been identified as potential modifiable factors that influence AD risk,[217,229] and increasing evidence from the PET literature suggest a complex relationship between cerebral Aβ and these modifiable factors.[230] In the preclinical phase of the disease, positive cognitive and physical lifestyle factors, such as higher levels of education, more lifetime cognitive engagement and increased exercise, have been associated with lower Aβ burden.[231–235,235a] Interestingly, most of these lifestyle characteristics have also been found to buffer the detrimental effects of *APOE* ε4 allele on Aβ burden.[236–238] Lifestyle might therefore mitigate Aβ-related genetic predispositions. Fig. 11 gives an example of how higher lifetime cognitive activity, a positive lifestyle factor, can mitigate the risk of Aβ deposition even in the presence of this major genetic risk factor.

An increasing number of neuroimaging studies point toward an important association of sleep with Aβ accumulation. In general, reports suggest that indicators of disturbed sleep such as shorter sleep duration, increased

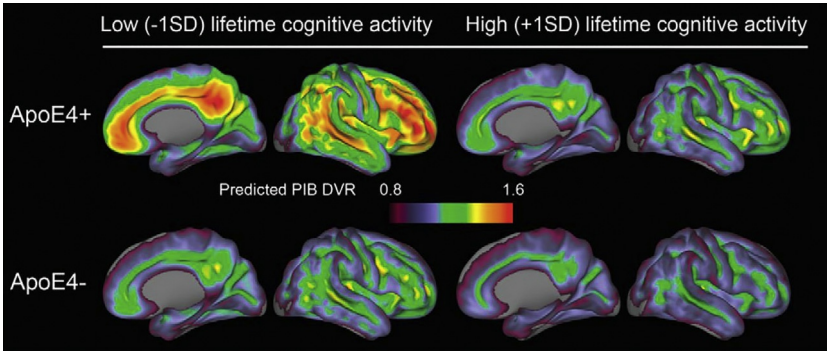

Fig. 11 Lifestyle can mitigate genetic risk. Visualization of the interaction between APOE ε4 carrier status and lifetime cognitive activity. Individuals carrying the APOE ε4 allele are at increased risk of developing Aβ pathology, but this effect is reduced by higher lifetime cognitive activity. *Figure adapted from Wirth M, Villeneuve S, La Joie R, Marks SM, Jagust WJ. Gene-environment interactions: lifetime cognitive activity, APOE genotype, and beta-amyloid burden.* J Neurosci. *2014;34:8612–8617.*

sleep latency or poor sleep quality are associated with increasing Aβ deposition in the brain.[239–242] Other treatable medical conditions such as obstructive sleep apnea and abnormal blood pressure during sleep are also related to brain Aβ levels.[243,244] Thus, sleep may play a critical role in the process of Aβ clearance from the brain.[245] However, increased sleepiness in older adults may not necessarily be beneficial for Aβ clearance, possibly because it may reflect underlying sleep disorders.[246] Furthermore, disturbed sleep may not only affect Aβ deposition but also contribute to the expression of associated cognitive symptoms.[247,248] Increasing sleep quality, even in conditions such as narcolepsy, may reduce Aβ accumulation,[249] so improving sleep in late-life may have important implications for future preventive interventions.

Finally, one major limitation of current AD PET imaging research is the underrepresentation of racial and ethnic minorities.[250,251] Further studies with racially and ethnically diverse samples are necessary to elucidate if the same genetic and modifiable factors influence Aβ-related risk across demographics.

7. Conclusion

The study of AD has been considerably accelerated in the last three decades as the field has developed disease biomarkers. Among these, radiotracers for molecular imaging of Aβ plaques have greatly contributed to our

understanding of disease etiology and the sequence of pathophysiological events leading up to AD dementia. PET studies have allowed researchers to posit that Aβ accumulation occurs over several decades without apparent immediate effects on cognitive performance or brain atrophy. Individuals with Aβ deposition, however, show cognitive decline and accelerated atrophy when followed over time. Thus, there seems to be a decades-long pre-symptomatic period that leads to clinical expression of the disease in which Aβ deposition may be an early event, but not necessarily the direct cause of brain and cognitive decline. The repeated failures of clinical trials of disease-modifying drugs may therefore owe, at least in part, to interventions being too little too late as massive brain changes have already occurred in cognitively impaired individuals. Thus, the pre-symptomatic phase holds tremendous potential for interventions aiming to prevent pathological accumulation of Aβ deposition or its associated brain changes even before Aβ occurs. One major hurdle to this approach remains the difficulty to identify Aβ-negative accumulators, a topic of high interest at the moment for the Aβ-imaging community. However, once identified, encouraging preventive lifestyle habits in at-risk individuals could achieve a 10% reduction in risk factors and prevent more than one million cases worldwide.[252]

Aβ-PET imaging will continue to hold an important role in future interventional studies for enrollment, evaluation of target engagement, and efficacy. Combining this modality with more recent imaging markers of disease processes (e.g., tau, neuro-inflammation) will also yield vital information regarding disease mechanisms and progression to identify viable targets and interventions which should, at long last, reduce AD morbidity.

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