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The ART of Loss: Aβ Imaging in the Evaluation of Alzheimer's Disease and other Dementias

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Abstract Molecular neuroimaging based on annihilation radiation tomographic (ART) techniques such as positron emission tomography (PET), in conjunction with related biomarkers in plasma and cerebrospinal fluid (CSF), are proving valuable in the early and differential diagnosis of Alzheimer's disease (AD). With the advent of new therapeutic strategies aimed at reducing β-amyloid (Aβ) burden in the brain to potentially prevent or delay functional and irreversible cognitive loss, there is increased interest in developing agents that allow assessment of Aβ burden in vivo. Aβ burden as assessed by molecular imaging matches histopathological reports of Aβ plaque distribution in aging and dementia and appears more accurate than FDG for the diagnosis of AD. Aβ imaging is also a very powerful tool in the differential diagnosis of AD from fronto-temporal dementia (FTD). Although Aβ burden as assessed by PET does not correlate with measures of cognitive decline in AD, it does correlate with memory impairment and rate of memory decline in mild cognitive impairment (MCI) and healthy older subjects. Approximately 30% of asymptomatic controls present cortical ^{11}C-PiB retention. These observations suggest that Aβ deposition is not part of normal ageing, supporting the hypothesis that Aβ deposition occurs well before the onset of symptoms and is likely to represent preclinical AD. Further longitudinal observations are required to confirm this hypothesis and to better elucidate the role of Aβ deposition in the course of Alzheimer's disease.

Keywords Alzheimer's disease · Aβ · Emission tomography · Neurodegenerative disorders · Brain imaging

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Loss

> all of this lucidity even now imperfectly preserved what memory will call up are not these images but a distillate: construct of mirror and shadow, of an intimate fact illuminating one nameless moment.
>
> Myrna Stone

Alzheimer's disease (AD), the leading cause of dementia in the elderly, is an irreversible, progressive neurodegener-

ative disorder clinically characterized by memory loss and cognitive decline [1]. It leads invariably to death, usually within 7–10 years after diagnosis. 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; burden which will only increase in the upcoming years [2–4]. Age is the dominant risk factor in sporadic AD. The progressive nature of neurodegeneration suggests an age-dependent process that ultimately leads to synaptic failure and neuronal damage in cortical areas of the brain essential for memory and higher mental functions [5, 6].

In the absence of biological markers, direct pathologic examination of brain tissue remains the only definitive method for establishing a diagnosis of AD [6, 7]. The typical macroscopic picture is gross cortical atrophy. Microscopically, there is widespread cellular degeneration and diffuse synaptic and neuronal loss, accompanied by reactive gliosis and the presence of the pathological hallmarks of the disease: intracellular neurofibrillary tangles (NFT) and extracellular amyloid plaques [6–8].

While NFTs are intraneuronal bundles of paired helical filaments mainly composed of the aggregates of an abnormally phosphorylated form of tau protein [9, 10], senile plaques consist of extracellular aggregates of amyloid β-peptide (Aβ) [11]. Aβ is a 4 kDa 39–43 amino acid metalloprotein product derived from the proteolytic cleavage of the amyloid precursor protein (APP), by β and γ-secretases [12]. To date, all evidential analysis strongly supports the notion that the breakdown of Aβ economy is central to AD pathogenesis [13]. The presence of extracellular Aβ in highly specialized cortical brain regions implicated in memory and cognition precede the other pathognomonic pathological features of AD, indicating that increases in Aβ are involved in the early presymptomatic stages of the disease. Compelling genetic data further support the Aβ theory [14–18]. To date four genes have been linked to autosomal dominant, early onset familial AD: APP, PS1, PS2 and ApoE, all of which lead to an increase in Aβ production.

The distribution and density of both diffuse and neuritic Aβ plaques [19] have not been consistently shown to correlate with the degree of cognitive impairment in AD [20, 21]. The best correlation has been observed with soluble levels of Aβ [19, 22–25] which is in equilibrium with insoluble Aβ in the plaques. The soluble oligomers of Aβ are neurotoxic through a number of possible mechanisms including: oxidative stress, excitotoxicity, energy depletion, toxic oxidative interaction with various metal species, inflammatory response and apoptosis. Nevertheless, the exact mechanism by which Aβ might produce synaptic loss and neuronal death is still controversial [1, 26, 27].

Currently, the clinical diagnosis of AD is based on progressive impairment of memory, decline in at least one other cognitive domain, and the exclusion of other diseases [28]. This approach is sensitive and specific enough for the diagnosis of AD only at the mid or late stages of the disease. Furthermore, a period of up to 5 years of prodromal decline in cognition, known as Mild Cognitive Impairment (MCI), usually precedes the formal diagnosis of AD [29, 30]. About 40–60% of carefully characterized subjects with MCI will subsequently progress to meet criteria for AD over a 3–4-year period [30, 31].

At this point there is no cure for AD. A deeper understanding of the molecular mechanism of Aβ formation, degradation and neurotoxicity is being translated into new therapeutic approaches [1, 27]. Most of the approved palliative treatment regimens involve the use of acetylcholinesterase inhibitors, glutamatergic agents, nonsteroidal anti-inflammatory drugs (NSAID), and antioxidants. The most promising approaches focus on reducing Aβ formation through secretase inhibitors or on increasing the removal of Aβ by immunotherapy or metal-protein attenuating compounds (MPAC) aimed at blocking the formation of Aβ oligomers and fibrils, inhibiting neurotoxicity [32, 33].

ART

Structural neuroimaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), are routinely used in the clinical evaluation of AD patients. Widespread cortical atrophy with a thinning of medial temporal lobe structures are the most consistent structural neuroimaging findings associated with AD [34], though not pathognomonic of the disease because there is overlap with normal aging. The fact that structural changes at visual inspection are not evident until late in the course of the disease has prompted the development and refinement of more sophisticated techniques, such as serial volumetric imaging and voxel compression subtraction, by emphasizing a quantitative approach capable of revealing subtle changes over time. The sophisticated and time-consuming nature of these procedures currently precludes their use as diagnostic tools for monitoring the patient with probable or possible AD. (for review see [35])

Modern functional neuroimaging techniques such as positron emission tomography (PET), single photon emission tomography (SPECT), magnetic resonance spectroscopy (MRS), functional magnetic resonance imaging (fMRI), MR Diffusion weighted imaging, and magnetoencephalography (MEG) have been developing new approaches to determine if an individual suffers from a particular form of dementia in addition to exploring the

molecular mechanisms of AD [35–37]. More sensitive than structural imaging modalities, functional neuroimaging approaches are capable of identifying subtle pathophysiologic changes in the brain before structural changes are present [38–44]. Functional neuroimaging thus possess greater potential for accurate and early diagnosis as well as monitoring of disease progression and therapeutic effects [45, 46]. Both PET and SPECT are molecular imaging techniques that use radiolabeled tracers to evaluate biological processes in vivo [45, 47–49]. These techniques already play an important role in the differential diagnosis of AD from other conditions such as vascular dementia, frontotemporal dementia (FTD), dementia with Lewy bodies (DLB) and depression [49, 50].

PET-or ART, as was once proposed-[51] is a sensitive molecular imaging technique that allows in vivo quantification of radiotracer concentrations in the picomolar range. PET radiotracers are typically designed to bind a substrate known to be involved in the biological process being evaluated. This interaction allows the in vivo assessment of the molecular processes at their sites of action, permitting detection of disease at asymptomatic stages, when there is no evidence of anatomic changes on CT and MRI [47].

Several studies have evaluated regional cerebral glucose metabolism with fluorodeoxyglucose (FDG) and PET. A typical pattern of reduced temporoparietal FDG uptake with sparing of the basal ganglia, thalamus, cerebellum, and primary sensorimotor cortex is typical of AD [50, 52, 53]. Due to its high sensitivity (94%) for detecting temporoparietal hypometabolism in patients with probable AD [50, 54, 55], FDG-PET might improve diagnostic and prognostic accuracy, thereby reducing both disease and treatment-related morbidity in patients with AD [56]. In a multicenter study, the prognostic value of FDG-PET showed a high degree of sensitivity (93%) and moderate specificity (73%) for prediction of progressive dementia [57]. Posterior cingulate and temporoparietal hypometabolism was observed in MCI patients when compared to controls. Progression of some of these patients to probable AD showed an additional bilateral hypometabolism in prefrontal areas, with further reductions in the posterior cingulate and parietal cortex, while no such changes were observed in the MCI group that remained stable [58].

Molecular imaging can also assess neurotransmitter systems in vivo. Nicotinic acetylcholine receptors (nAChRs) have been implicated in a variety of central processes, such as memory and cognition [59, 60]. Abnormally low densities of nAChRs have been measured in vitro in autopsy brain tissue of AD patients [61, 62]. Only PET studies using ^{11}C-nicotine found reduced uptake and binding in the temporal and frontal cortices of AD patients [60, 63]. While tacrine or rivastigmine treatment increased uptake of ^{11}C-nicotine to the brain paralleled by improvement in neuropsychological performance in AD patients [64–66] similar findings were not observed when AD patients were treated with galantamine [67, 68]. Although the main focus of neuroceptor studies in AD has been the study of nAChRs, muscarinic acetylcholine receptors (mAChRs), especially M1 and M2 mAChRs subtypes, have also been implicated in AD [69–71]. M1 mAChRs agonists and M2 mAChRs antagonists have been shown to improve cognition by their cholinomimetic effect increasing ACh release in addition to their direct action on the enzymes cleaving Aβ [70–74]. Highly selective subtype-specific radioligands for M1 or M2 mAChRs are not yet available [75], but radiotracers that can assist in both quantifying mAChRs receptor densities and monitoring AD therapy are being developed [76]. Several other neurotransmitter/neuroreceptor systems have also been evaluated in dementing neurodegenative diseases [77–83].

The ART of Loss

Insights into the molecular mechanisms of AD pathogenesis not only open new opportunities for the successful development of neuroprotective treatment strategies aimed at the prevention of Aβ generation and deposition, but also enable the development of new neuroimaging approaches [1, 33, 84, 85]. While clinical criteria together with current structural neuroimaging techniques (CT or MRI) are sufficiently sensitive and specific for the diagnosis of AD at the mid or late stages of the disease, the development of a reliable method of assessing Aβ burden in vivo will permit early diagnosis at presymptomatic stages, more accurate differential diagnosis, as well as allowing monitoring of disease-modifying therapy [1, 85] (Table 1).

Aβ plaques and NFTs are the hallmark brain lesions of AD. These microscopic aggregates are still well beyond the resolution of conventional neuroimaging techniques used for the evaluation of patients with AD. Selective tau imaging, for in vivo NFT quantification, is still in its early stages of development [86]. Since Aβ is at the centre of AD pathogenesis, and given that several pharmacological

Table 1 Potential roles for Aβ imaging

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

agents aimed at reducing Aβ levels in the brain are being developed and tested, many efforts have focused on developing radiotracers or agents that allow Aβ imaging in vivo [46, 87]. For a radioligand to be useful as a neuroimaging probe for Aβ, a number of key general properties must be present. These ideal Aβ probes must be lipophilic molecules that cross the blood brain barrier, are preferably not metabolized, and reversibly bind to Aβ in a specific and selective fashion. (Table 2) Several compounds have been evaluated as potential Aβ probes: derivatives of histopathological dyes such as Congo red, Chrysamine-G, thioflavin S and T [88–101], NSAID derivatives [100, 102–105], as well as self-associating Aβ fragments [106–108], anti-Aβ antibodies or antibodies fragments [109–111], serum amyloid P and basic fibroblast growth factor [112]. Some of the same PET radiotracers are being evaluated as MR contrast agents for imaging plaques in transgenic mice [113–118].

While all of the aforementioned tracers bind with varying degrees of success to Aβ fibrils and brain homogenates of AD patients, Congo Red and thioflavin T and some of their derivatives have recently been shown to also bind to soluble oligomeric forms of Aβ [119]. On the other hand, Aβ soluble species represent less than 1% of the total brain Aβ [19, 85], and the reported affinity of the currently most successful of the tested Aβ imaging agents, (N-Methyl)2-(4-methylamino-phenyl)-6-hydroxy-benzothiazole (6-OH-BTA-1, a.k.a. Pittsburgh Compound B or PiB) [120] for these soluble oligomers seems to be significantly lower than for Aβ fibrils [119, 121, 122]. Until highly specific radiotracers are developed to selectively bind the Aβ soluble species, the contribution of these binding to the PET signal from tracers such as ^{11}C-PiB is considered negligible [85].

Quantitative imaging of Aβ burden in vivo is allowing the relationship between Aβ burden and clinical and neuropsychological characteristics in AD to be defined. Only a handful of agents have found their way into human clinical trials. The first human studies were carried out with ^{18}F-FDDNP, tracer characterized for binding to both plaques and NFTs [123]. Amyloid imaging studies have been conducted in AD patients and normal controls using ^{11}C-SB13 [124], ^{11}C-BF227 [125], ^{123}I-CQ [126], and ^{123}I-IMPY [127]. ^{11}C-PiB, the most successful of the currently available amyloid tracers, is a derivative of thioflavin T that has been shown to possess high affinity and high specificity for Aβ fibrils [93, 94, 128–130]. More recently, the refinement of in vitro methods that are more pertinent to ^{11}C-PIB binding in vivo, have provided further insight into ^{11}C-PIB-PET retention. Studies conducted by Lockhart et al (2007) have revealed that PiB, in addition to binding classical fibrillar Aβ plaques, binds a range of Aβ containing lesions including diffuse plaques and cerebrovascular amyloid angiopathy [131]. Until microPET evaluations in transgenic mice models of AD were performed with high specific activity ^{11}C-PiB (>200 GBq/μmol), showing ^{11}C-PiB retention co-localizing with plaques [132], it was thought that ^{11}C-PiB did not significantly bind to aggregated Aβ in transgenic mouse brain [121, 133]. It was also reported that ^{11}C-PiB preferably binds one kind of the *N*-terminal truncated $Aβ_{1–42(43)}$ species in senile plaques, more specifically the one truncated at position 3 (Aβ3(pE)), displaying a fivefold higher affinity for $Aβ3(pE)_{1–42(43)}$ than for $Aβ_{1–42(43)}$ [132]. This is relevant because the accelerated formation of plaques seems to be associated with this $Aβ3(pE)_{1–42(43)}$ species [134, 135].

PET studies in human subjects have shown a robust difference between the retention pattern in AD patients and healthy controls, with AD cases showing significantly higher retention of ^{11}C-PiB in neocortical areas of the brain affected by Aβ deposition [120, 124, 136–138]. ^{11}C-PiB is also elevated in subjects diagnosed with cerebrovascular amyloid angiopathy [139], showing a similar distribution to AD and DLB cases [140]. Human PET studies have also demonstrated a correlation between ^{11}C-PiB binding and the rate of cerebral atrophy in AD subjects [141], and with decreased cerebrospinal fluid (CSF) $Aβ_{1–42}$ in both demented and non-demented subjects [142]. Multimodality studies in early AD have shown Aβ deposition in posterior cortical regions that are associated with memory retrieval in young adults [138]. Additionally, this deposition is inversely correlated with activation of language centers, leading to a functional reorganization of the language system [143].

To date, we have evaluated more than 220 subjects to investigate the relationship between Aβ deposition in vivo using ^{11}C-PiB PET and clinical features in patients with various dementias, mild cognitive impairment and age-matched healthy control subjects [136]. Our initial 70 subjects underwent a 90 min dynamic PET scan after administration of ^{11}C-PiB. These initial studies showed that ^{11}C-PiB binding was reversible, clearing fastest from cerebellum and slowest from white matter, in agreement with the first published reports [120, 144]. Clearance from cerebellar cortex was the same for all groups [136]. Figure 1

Table 2 Ideal amyloid-β radiotracer

Easily labeled with ^{18}F, ^{99m}Tc, ^{123}I
Lipid soluble (crosses BBB)
High affinity and selectivity for Aβ plaques
Slow dissociation from binding site
Rapidly cleared from blood
Not metabolized
Provide quantitative and reproducible information about Aβ burden in the brain

demonstrates ^{11}C-PiB binding for each group. On visual inspection of all our studies we observed that cortical PiB binding, regardless of disease severity, was markedly elevated in all but one AD subject, and it was generally lower and more variable in DLB. (Figure 1) The regional brain distribution was similar in both AD and DLB being greatest in frontal, cingulate, precuneus, striatum, parietal, and lateral temporal cortex. Occipital cortex, sensori-motor cortex and mesial temporal cortex were less affected. There was no cortical ^{11}C-PiB retention in FTD, and about 30% of asymptomatic age-matched healthy controls (HC) presented cortical ^{11}C-PiB retention. (Figure 1) Subjects in classified as MCI presented either an "AD-like" or "HC-like" pattern of cortical ^{11}C-PiB retention. (Figure 1)

Aβ burden is usually quantified through distribution volume ratios (DVR) or standardized uptake value ratios (SUVR). DVR are calculated through graphical analysis using dynamic data acquired for 90 min and using the cerebellum as reference region [136, 144, 145], while SUVR are defined as the region to cerebellum ratio at 40–60 or 40–70 min post injection [146, 147]. Aβ burden as measured both by DVR and SUVR was significantly higher in AD when compared to HC, FTD and MCI subjects. (Figure 1) A strong correlation was observed between SUVR and DVR for all regions (r=0.75–0.94), with the strongest correlations between SUVR and DVR observed in cortical and subcortical gray matter regions (r=0.95–0.98) and the lowest correlations in midbrain and pons (r=0.75 and 0.78, respectively). Based on ROC analysis comparing HC subjects and AD patients, a SUVR threshold of 1.60 was selected to define PiB-positive and PiB-negative SUVR values [148]. SUVR values provide reliable quantification of Aβ burden and can be obtained from a single 30-min ^{11}C-PiB PET scan, making it a much more suitable approach to Aβ quantification in clinical studies, particularly in the elderly and cognitively impaired who may not be able to tolerate a prolonged scan.

Due to similar and high cortical ^{11}C-PiB-PET retention in AD and DLB subjects, and given that PiB is a derivative of thioflavin-T that binds to β-sheet structures [149], we deemed it crucial to characterize the potential binding of PiB to α-synuclein in DLB patients [150]. Analysis of the in vitro binding studies indicated that ^{3}H-PiB binds to α-synuclein fibrils; but with lower affinity than that reported for $A\beta_{1-42}$ fibrils [122]. ^{3}H-PiB was observed to bind to Aβ plaque-containing DLB brain homogenates, but failed

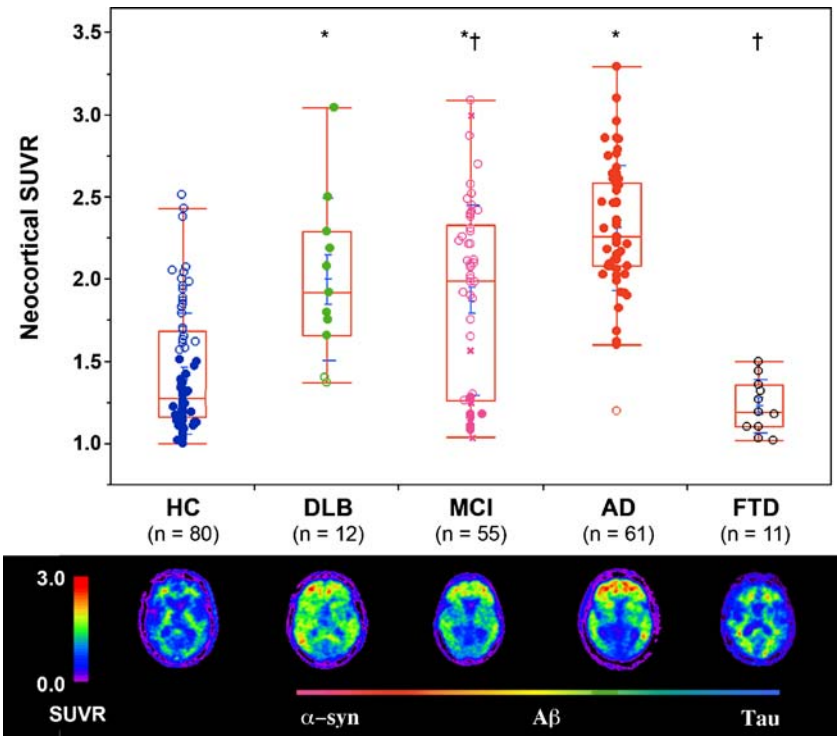

Fig. 1 *Top panel*: Box-and-whiskers plot of neocortical Aβ burden as quantified by ^{11}C-PiB $SUVR_{40–70}$ for Alzheimer's disease (AD), Dementia with Lewy Bodies (DLB), frontotemporal dementia (FTD), Mild Cognitive Impairment (MCI), and healthy controls (HC). *Open circles* in the HC group represent those participants classified as PiB-positive. In the MCI group, *open circles* represent amnestic MCI; full circles nonmemory single domain MCI; and "*x*" indicates nonmemory multiple domain MCI. In both the AD and DLB group, *open circles* represent PiB-negative participants. *Bottom panel*: Representative transaxial ^{11}C-PiB PET images of HC, and subjects affected by the toxic gain of function of misfolded proteins, such as α-synuclein for DLB, Aβ for AD and MCI, and tau for AD and FTD. *Asterisk* Significant results compared to controls (p<0. 01) *dagger* Significant results for MCI, DLB and FTD compared to AD (p<0. 01)

to bind to DLB homogenates that were Aβ plaque-free ('pure DLB'). Positive PiB fluorescence staining of DLB brain sections co-localised with immunoreactive Aβ plaques, but failed to stain Lewy bodies, while image quantification analysis suggested that given the small size and low density of Lewy bodies within the brains of DLB subjects, any contribution of Lewy bodies to the ^{11}C-PiB-PET signal would be negligible.[150] These studies indicate that PiB retention observed within the cortical grey matter regions of DLB subjects in ^{11}C-PiB PET studies is largely attributable to PiB binding to Aβ plaques and *not* Lewy bodies [150]. These findings were further confirmed by a preliminary report on Parkinson's disease (PD) patients [151], and studies using ^{11}C-PiB PET to discriminate between AD, PD, DLB and patients with Parkinson's disease and dementia [152]. Additionally, Aβ burden in DLB patients is inversely correlated with the interval from onset of cognitive impairment to the full development of the DLB characteristic phenotype [136], consistent with the role of Aβ in promoting aggregation and exacerbation of α-synuclein dependent neuronal injury [153]. In a similar way that with α-synuclein fibrils [150], PiB binds to NFTs with comparatively lower affinity than Aβ [131], further confirming that in vivo ^{11}C-PIB cortical uptake primarily reflects Aβ-related cerebral amyloidosis.

To date, none of the FTD subjects we have studied, have exhibited cortical ^{11}C-PiB binding [136] (Fig. 1). While in the majority of cases ^{11}C-PiB cannot discriminate AD from DLB, it seems to be the perfect tool to reliably differentiate AD from FTD [136, 154–156].

Approximately 30% of HC subjects exhibited cortical binding, predominantly in the prefrontal cortex and posterior cingulate/precuneus areas with some of them displaying the same degree of retention as observed in AD subjects, (Fig. 2) consistent with a previous preliminary report [157]. The demonstration of ^{11}C-PiB binding in a proportion of HC support post mortem observations that Aβ aggregation predominantly occurs before the onset of dementia [136, 157–160].

Another strong indicator that Aβ aggregation occurs before the onset of dementia was hightlighted when subjects from the longitudinal Melbourne Healthy Ageing Study (MHAS) [161, 162] were studied with ^{11}C-PiB. In this study, Aβ burden as measured by ^{11}C-PiB-PET, was compared with the results of cognitive testing performed on 35 elderly participants (age 73±6 years old) who were classified as being either cognitively "stable" or "declining" based on clinical assessment and annual word-list recall scores from the preceding 7–10 years before their PET scans. Rates of decline were calculated from the word-list recall scores. Twelve subjects were classified as declining. At the time of the PET scan, four subjects had MCI, one had AD, and seven presented cognitive decline even though they remained within the normative range. Declining subjects were much more likely to show cortical PiB retention than stable subjects: 8 of the 12 declining subjects compared with 4 of the 23 stable subjects had cortical PiB binding. Neocortical Aβ burden as measured by ^{11}C-PiB SUVR, correlated with episodic memory impairment, disease severity as measured by MMSE and rate of decline. No correlations were found in the stable group alone. When the 12 participants in the declining group were evaluated separately, the correlations with episodic memory impairment, disease severity and rate of decline persisted [163].

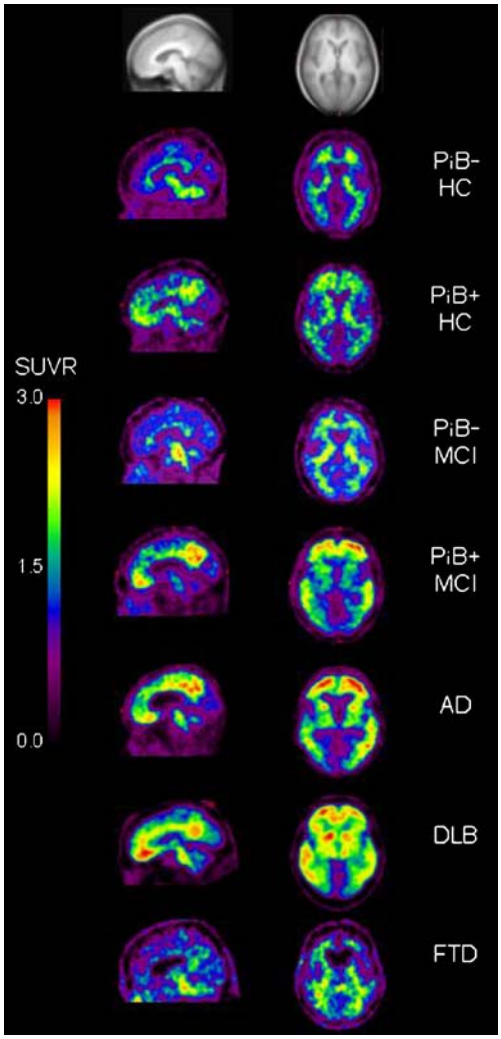

Fig. 2 In vivo imaging of Aβ burden in ageing and dementia. Representative sagittal (*left panel*) and transaxial PET images (*right panel*) of a 75 year-old PiB-negative healthy control (PiB −HC) subject (MMSE 29), a 77 year-old PiB-positive healthy control (PiB +HC) subject (MMSE 28), an 83 year-old PiB-negative subject with mild cognitive impairment (PiB −MCI) (MMSE 28), an 82 year-old PiB-positive subject with mild cognitive impairment (PiB +MCI) (MMSE 28), a 76 year-old Alzheimer's disease (AD) patient (MMSE 21), a 78 year-old patient with dementia with Lewy Bodies (DLB) (MMSE 19), and an 59 year-old patient with frontotemporal dementia (FTD; MMSE 25)

Furthermore, analysis of ^{11}C-PiB binding in subjects diagnosed with MCI, a condition that progresses to AD at a rate of approximately 15% per year [31, 164], revealed two distinct accumulation patterns. Sixty-three percent of MCI cases showed cortical ^{11}C-PiB binding similar in distribution and sometimes in degree as AD, while the other 37% showed no cortical binding, similar to HC. (Figure 2) Interestingly, all the subjects classified as nonamnestic single-domain MCI and 66% of the subjects classified as nonamnestic multiple-domain MCI [165] were ^{11}C-PiB-negative. Only 22% of amnestic MCI subjects were deemed ^{11}C-PiB-negative. There was a strong relationship between impaired episodic memory performance and Aβ burden in MCI (Fig. 3), a feature not present in the AD group [147]. Ongoing longitudinal follow-up studies will permit full elucidation of the significance of ^{11}C-PiB binding in the elderly controls and MCI subjects. A preliminary report has shown that 7 of 21 MCI subjects converted to AD within 2–16 months after their PiB PET scan [166]. MCI "converters" showed a higher PiB retention than "non-converters", and their PiB retention highly correlated with CSF biomarkers and episodic memory [166]. We have observed very little change in Aβ burden in 57 subjects (28 HC, 11 MCI and 18 AD) in follow-up ^{11}C-PiB-PET studies approximately 21 months apart, with an overall increase in Aβ burden of 6.2% in the AD group, slightly below the reported test–retest reproducibility for ^{11}C-PiB PET studies [144, 146, 167, 168]. Both the HC and the MCI groups showed almost no change (0.9% and 2.4%, respectively). This finding is somewhat in contrast with a recently reported 2-year follow-up study in AD subjects where, despite some participants presenting cognitive decline and

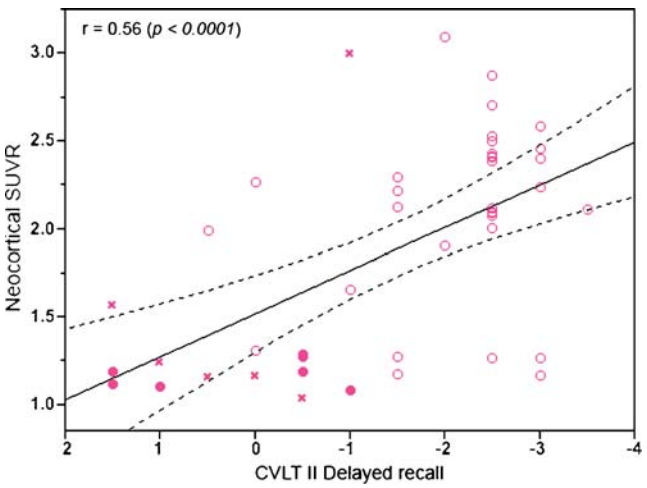

Fig. 3 A significant correlation was observed between Aβ burden as measured by PiB SUVR and memory impairment (standard scores on delayed recall from the California Verbal Learning Test-Second edition) in MCI subjects. Open circles represent amnestic MCI. Full circles represent nonmemory single domain MCI, while x indicates nonmemory multiple domain MCI

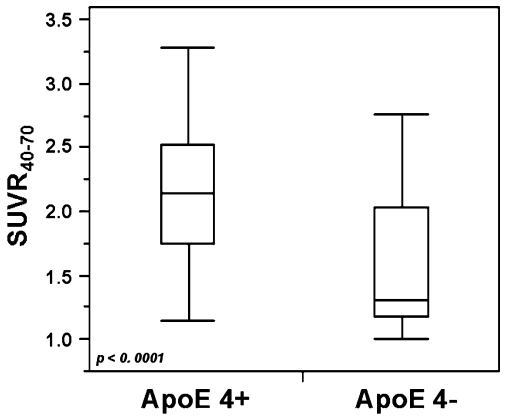

Fig. 4 Box-and-whiskers plot of neocortical Aβ burden as quantified by ^{11}C-PiB $SUVR_{40–70}$ for ApoE ε4+ and ApoE ε4-subjects. ApoE ε4+ subjects showed a significantly higher (p<0.0001) Aβ burden than ApoE ε4-individuals

increased FDG hypometabolism, there was stable or even decreased ^{11}C-PiB binding [167]. On the other hand, and based on our own follow-up studies, 10 out of 18 MCI subjects that 'converted' to AD were ^{11}C-PiB-positive on their baseline study. These findings, in addition to the evidence of Aβ deposition in a high percentage of MCI and asymptomatic HC, suggest that Aβ is an early and necessary, though not sufficient, cause for cognitive decline in AD. Maybe specific in vivo tau amyloid imaging will help elucidate this persistent decline in cognitive function.

In contrast to the rare, early-onset autosomal dominant forms of AD, the only consistent genetic marker for both the early-onset familial and late-onset non-familial form of

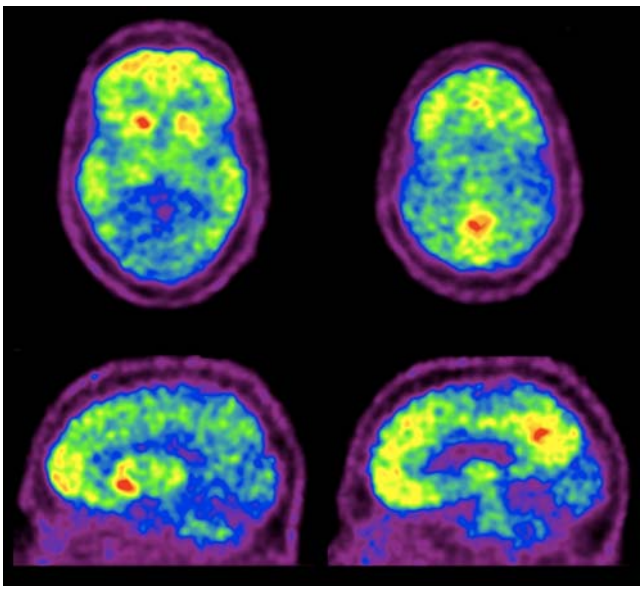

Fig. 5 Representative PiB PET images of an individual carrier of a familiar APP V717L mutation. PiB binding was highest in the caudate nuclei and posterior cingulate. PiB binding was also observed in the prefrontal cortex

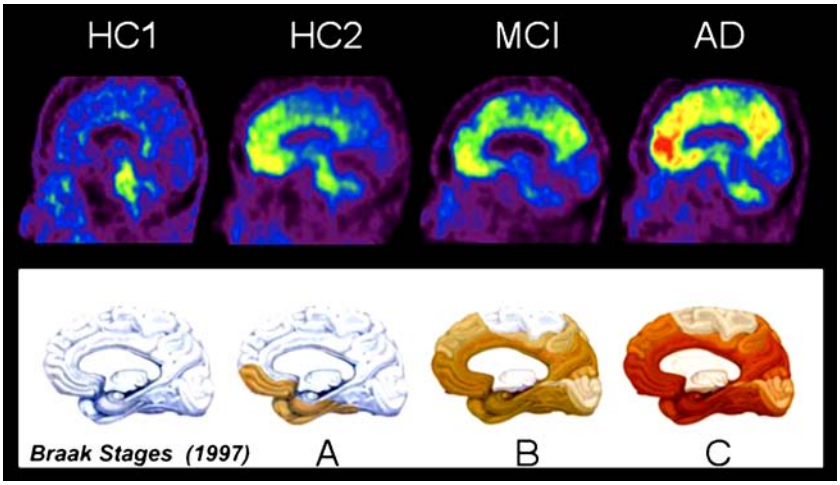

Fig. 6 Representative sagittal PET images showing the regional uptake of ^{11}C-PiB, reflecting Aβ burden in the brain, in two asymptomatic healthy age-matched controls (*HC1* and *2*), a participant with mild cognitive impairment (*MCI*), and a participant with Alzheimer's disease (*AD*; *top panel*), and schematics showing the stages of Aβ deposition in the human brain as proposed by Braak and Braak (*bottom panel*) [172]. The images demonstrate a marked difference in ^{11}C-PiB regional distribution between an HC1 subject and an AD patient, with highest ^{11}C-PiB accumulation in frontal and posterior cingulate/precuneus areas. The MCI subject presents lower ^{11}C-PiB accumulation, though in a similar pattern, than the AD patient. Note that HC2 shows cortical PiB accumulation in the orbitofrontal and cingulate gyrus

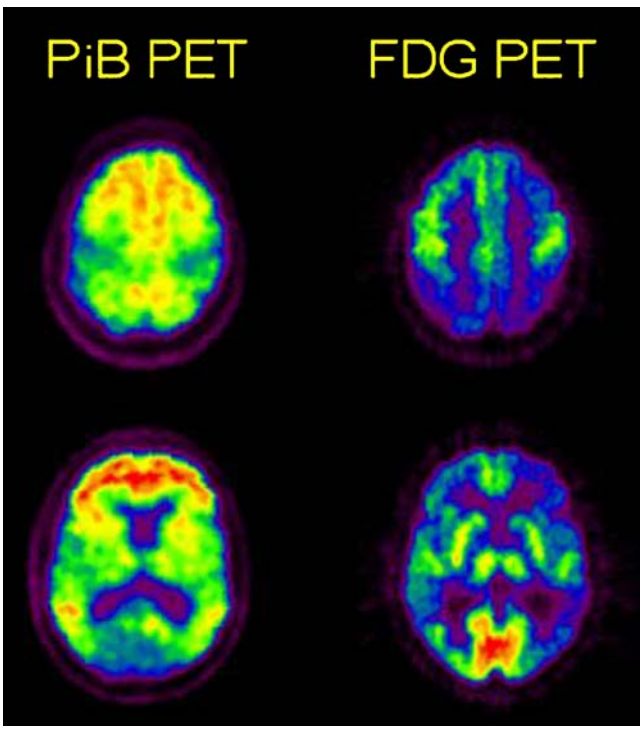

Fig. 7 Typical PiB (*left panel*) and FDG (*right panel*) PET images in a 82 year-old Alzheimer's disease patient. PiB PET images show radiotracer retention in frontal, temporal and cingulate cortices as well as in the caudate nuclei. FDG PET images show an *inverted* pattern, with areas of glucose hypometabolism matching the areas of high PiB binding

dementia is the polymorphism of apolipoprotein E (ApoE) allele on chromosome 19 [169, 170]. Examination of ApoE ε4 allele status revealed that ε4 carriers presented significantly higher ^{11}C-PiB binding than non-ε4 carriers. (Figure 4) PET images of a preclinical familial case with an APP V171I mutation revealed very high retention in the caudate nuclei and the posterior cingulate/precuneus area and, to a lesser degree, in prefrontal and temporal cortices (Fig. 5) in concordance with previous reports of subjects with PS1 mutations [171].

Both quantitative and visual assessment of ^{11}C-PiB-PET images show a pattern of ^{11}C-PiB retention that seems to replicate the sequence of Aβ deposition found at autopsy [172, 173], with initial deposition in orbitofrontal cortex and gyrus rectus, followed by the posterior cingulate/precuneus, the rest of the prefrontal cortex and lateral temporal cortex, and finally to the parietal cortex. (Figure 6) Furthermore, the percentage of ^{11}C-PiB-positive subjects increases each decade at the same rate as that observed in autopsy studies reported 20 years ago [174].

Table 3 Comparison of PiB and FDG for the diagnosis of Alzheimer's disease

	Sensitivity	Specificity	Accuracy	Reader agreement (κ)
PiB Visual	0.98	0.89	0.90	0.84
FDG Visual	0.80	0.68	0.72	0.56
PiB SUVR	1.00	0.92	0.95	
FDG SUVR	0.92	0.80	0.86	

Visual assessment of ^{11}C-PiB-PET images by clinicians blinded to the diagnosis were >90% sensitive and specific for AD. The accuracy of visual assessment was very similar to that obtained by quantitative analysis. ^{11}C-PiB retention in AD matched the regional hypometabolism observed in FDG images. (Figure 7) When compared to FDG, visual agreement between blinded assessors was excellent for ^{11}C-PiB and less consistent for FDG (Kappa=0.90 and 0.56, respectively). ^{11}C-PiB was more accurate than FDG for the diagnosis of AD, with an accuracy of ~90% and ~70%, respectively. (Table 3) ^{11}C-PiB binding in parietal cortex appeared more specific for AD than binding in other regions. Furthermore, visual reading of a 30-min ^{11}C-PiB acquisition beginning 40 min post injection had similar accuracy to quantitative analysis of a 90-min dynamic scan [148]. Additionally, the presence of Aβ was demonstrated in four patients with atypical onset of dementia who presented with provisional diagnosis of either progressive non-fluent aphasia—considered by many as a variant of FTD-or posterior cortical atrophy, respectively. ^{11}C-PiB-PET has the potential to facilitate differential diagnosis of dementia and therefore be useful in identifying patients who could benefit from specific therapeutic strategies aimed at the reduction of Aβ [175].

In vivo amyloid imaging with PET is allowing new insights into Aβ deposition in the brain, facilitating research into the causes, diagnosis and future treatment of dementias, where Aβ may play a role. Among the caveats of this imaging approach is that PiB is labeled with C-11, therefore requiring a cyclotron in situ, and limiting its clinical application. The development of specific F-18 [98], I-123 [176], or Tc-99m [177] labeled Aβ ligands will allow widespread application of the technique, the same way FDG is presently applied for cancer studies. Novel F-18 ligands are already being tested in phase I clinical studies [178, 179].

Lost and Found

Despite the promise of recent advances in molecular neurosciences, the early detection of neurodegenerative diseases like AD, especially the identification of at-risk individuals before the development of the typical phenotype, still requires several biomarkers to ensure presymptomatic diagnosis and ultimately, intervention with disease-modifying medications during the presymptomatic period [1, 180, 181]. Frank et al. state that "The ideal biomarker for AD should detect a fundamental feature of neuropathology and be validated in neuropathologically confirmed cases; it should have a diagnostic sensitivity >80% for detecting AD and a specificity of >80% for distinguishing other dementias; it should be reliable, reproducible, noninvasive, simple to perform, and inexpensive." [182] Amyloid imaging with PET imaging fulfills most of these criteria.

Amyloid imaging findings match histopathological reports of Aβ distribution in aging and dementia and it appears more accurate than FDG for the diagnosis of AD, particularly in older subjects [148]. Although β-amyloid imaging with PET has proven to be an excellent approach in the differential diagnosis of AD from FTD [136], its application should not be limited to its ability for differential diagnosis. As new treatments in clinical trials are aimed at preventing or slowing AD progression, either by preventing Aβ generation or deposition, or increasing the clearance of Aβ [32, 183–186], the role of imaging and quantifying Aβ burden in vivo is becoming increasingly crucial, being acknowledged as part of the diagnostic evaluation of dementia [187]. Although these treatments are aimed at AD, our findings suggest that they may have value in other dementias such as DLB, where Aβ deposition is present. The ability to detect preclinical or early stage disease through clinical, laboratory, and neuroimaging tests, allows the customization and monitoring of treatment. Early identification of the at-risk individual means anti-Aβ therapy can be administered at a time when the disease burden is mild and it may prevent or delay functional and irreversible cognitive losses.

Amyloid imaging seems to be the ideal approach to evaluate MCI subjects. Although Aβ burden as assessed by ^{11}C-PiB-PET does not correlate with cognitive decline in AD, it does correlate with memory impairment and the rate of memory decline in the ageing population and MCI subjects [147]. Furthermore, about 20–30% of HC present cortical ^{11}C-PiB retention [136, 157]. Hence, these observations suggest that Aβ deposition is not part of normal ageing, supporting the hypothesis that Aβ deposition occurs well before the onset of symptoms and is likely to represent preclinical AD. Additionally, further longitudinal observation, coupled with different tracers (e.g. selective tau ligands) and biomarkers (e.g. titration of tau and Aβ in CSF and blood) are required not only to confirm this hypothesis, but also to better elucidate the role of Aβ deposition in the course of Alzheimer's disease.

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