

## Review Article

# <sup>18</sup>F-labeled radiopharmaceuticals for the molecular neuroimaging of amyloid plaques in Alzheimer's disease

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**Abstract:** Alzheimer's disease (AD) is the most common cause of dementia in the elderly, with tremendous impact on the affected individuals and the society. Definitive diagnosis can be achieved only by post mortem examination. Clinical diagnosis criteria currently applied in clinical practice for AD often fail to accurately discriminate between AD and non-AD dementia with up to 40% of misdiagnosed patients. Several published papers demonstrated that the pre-clinical phase of AD is characterized by an early rise in beta-amyloid accumulation into inter-neuronal space, followed by a severe synaptic dysfunction. Thus, beta-amyloid protein, detected in the cerebrospinal fluid, has been considered a specific AD biomarker. Molecular imaging of beta-amyloid deposits, with positron emission tomography (PET) and <sup>18</sup>F-labeled radiopharmaceuticals such as <sup>18</sup>F-florbetapir, <sup>18</sup>F-florbetaben, and <sup>18</sup>F-flutemetamol, has emerged as potential powerful tool for aiding AD diagnosis. The aim of the present paper is to review the existing literature on the clinical use of these new amyloid tracers in order to delineate their diagnostic value and limitations.

**Keywords:** PET, amyloid plaques, Alzheimer's disease, neuroimaging

## Introduction

Alzheimer's disease (AD) represents the most common cause of dementia worldwide and its global burden is expected to grow further due to population's aging. It is characterized by early deficits in memory which inevitably progress to severe and generalized cognitive deterioration. The annual incidence of AD increases with age; it has been reported an incidence of 53 new cases per 1000 people aged 65 to 74, 170 new cases per 1000 people aged 75-84, and 230 new cases per 1000 people aged over 85 [1]. Thus, AD represents a critical public health issue in many countries around the world, with a tremendous impact on the society.

As concerns its etiopathology, in most of the cases AD occurs sporadically with late onset and multi-factorial in etiology [2]. Definitive diagnosis of AD is based on the post mortem examination. Therefore, the initial diagnosis is presumptive and made by clinical evaluation

and neuropsychological testing. Conventional neuroimaging with magnetic resonance (MRI) presents some limitations, especially in terms of specificity, in the diagnosis of AD [3]. Furthermore, a variety of clinical conditions can mimic AD and, according to several published reports, between 12% and 23% of patients diagnosed with AD resulted to be misdiagnosed at the autopsic examination [4]. The most common features leading to definitive AD diagnosis consist of general atrophy of the cortex, neuron and synapse loss, extracellular plaques composed of insoluble beta-amyloid (A $\beta$ ) and intraneuronal neurofibrillary tangles (NFTs).

Several scientific evidences indicate that the pathogenesis of AD is driven by the progressive accumulation of A $\beta$  peptide into the inter-neuronal space [5]. Although the pathogenetic pathways leading to AD are certainly very complex involving several mechanisms such as the dysfunction in cholinergic neurons and the aberrant aggregation of hyperphosphorylated tau protein, it has been demonstrated that the

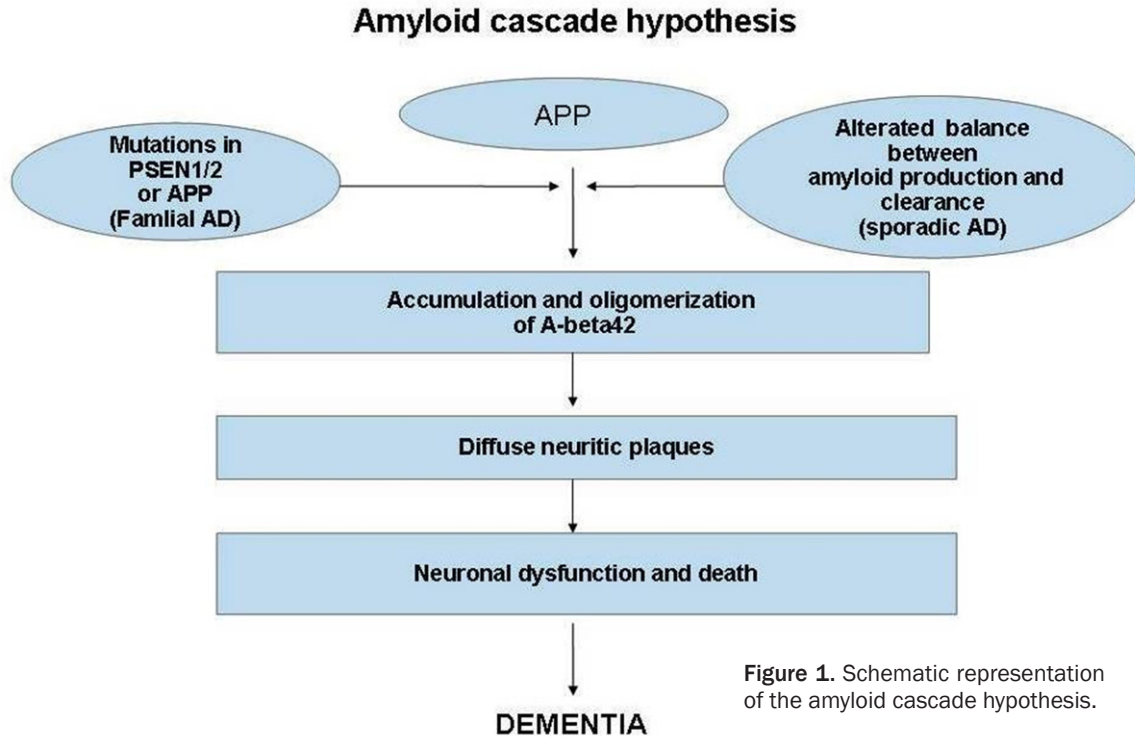


Figure 1. Schematic representation of the amyloid cascade hypothesis.

amyloid cascade plays a fundamental role [6]. Cerebrospinal fluid levels of beta-amyloid is clinically used as AD biomarker since altered levels of this peptide are highly associated with conversion of presymptomatic patients to AD [7].

It has to be pointed out that the Abeta peptide has represented also the most studied target for the neuroimaging of AD. The identification of amyloid deposits, with positron emission tomography (PET) and <sup>18</sup>F-labeled radiopharmaceuticals such as <sup>18</sup>F-florbetapir, <sup>18</sup>F-florbetaben, and <sup>18</sup>F-flutemetamol, has been recently introduced as potential powerful tool for aiding clinicians in AD diagnosis.

The purpose of this paper is to review the existing literature on the clinical use of these new amyloid-tracers in order to delineate their diagnostic value and limitations.

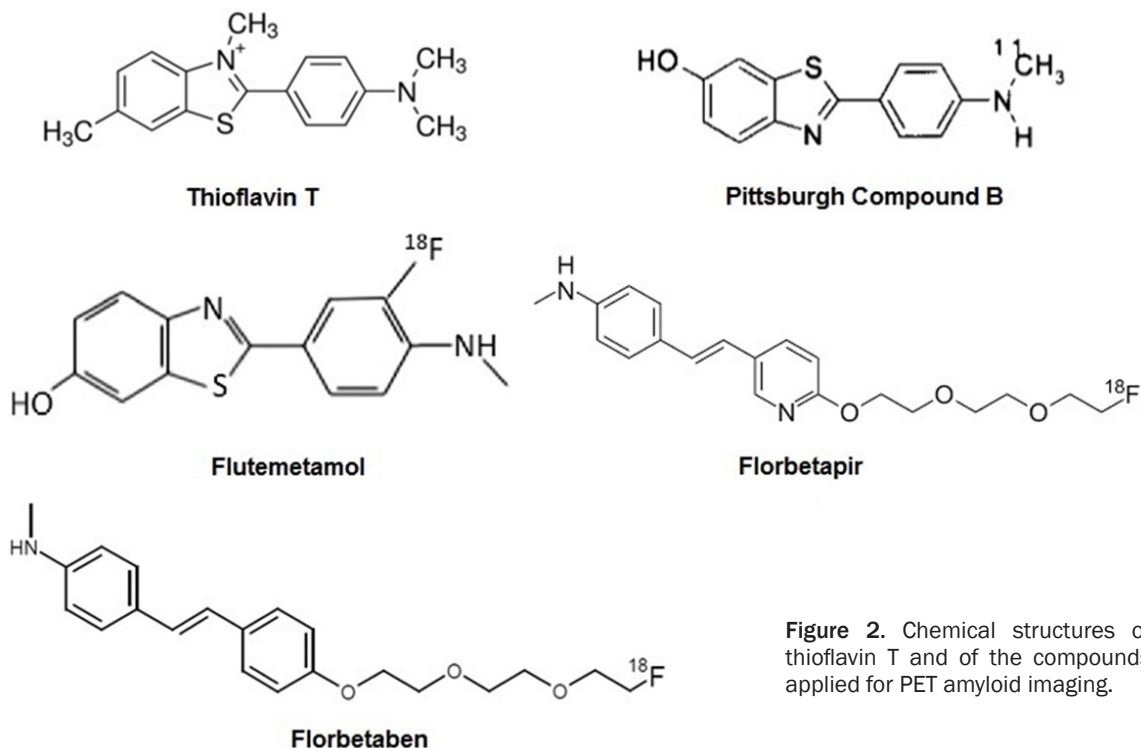
*The amyloid cascade hypothesis in AD pathogenesis*

The amyloid cascade hypothesis is based on the assumption that AD pathogenesis is due to a series of abnormalities in the production and in the secretion of the amyloid precursor pro-

tein (APP). APP is a transmembrane glycoprotein with a still unclear role in cell function. APP is sequentially processed through a series of cleavages operated by beta- and gamma-secretases. In particular, gamma-secretase is a high molecular weight complex minimally composed of four components: presenilins (PSEN), nicastrin, anterior pharynx defective 1, and presenilin enhancer 2 [8]. Gamma-secretase cuts the gamma-site of carboxyl-terminal fragment of APP producing the 2 major Abeta isoforms: Abeta42 (42 residues long) and Abeta40 (40 residues long).

Concentrations of amyloid in brain are the consequence of the balance between production and clearance; in AD patients, a not fully understood mechanism leads to an abnormal accumulation of amyloid beta. Abeta42 isoform is the major component of amyloid plaques due to its low solubility and propensity to form aggregates with beta-pleated sheet structure [9]. Extracellular Abeta oligomers bind the cell surface, leading to functional disruption of a number of receptors, thus producing dysfunction and neurodegeneration (Figure 1) [10].

The role and the importance of biomarkers for the correct framework of AD have been recently



**Figure 2.** Chemical structures of thioflavin T and of the compounds applied for PET amyloid imaging.

underlined by the taskforce organized by the National Institutes of Aging and the Alzheimer's Association (NIA-AA). It has been proposed, in fact, that the diagnosis of AD should be based on the presence or absence of a well defined biomarker system instead of clinical symptoms [11]. This biomarker system, termed AT (N), includes three hallmarks typical of AD. The biomarkers in the A group are representative of the amyloid burden and can be evaluated by either PET imaging with amyloid tracers or measuring the levels of Abeta isoforms in the cerebrospinal fluid. The biomarkers in the T group reflect the aggregated tau proteins and can be determined by measuring hyperphosphorylated tau proteins in cerebrospinal fluid and also with PET radioligands specifically binding to tau deposits in brain. Finally, the biomarkers in the N group are indicative of neurodegeneration and include atrophy on MRI and hypometabolism on  $^{18}\text{F}$ -Fluoro-deoxy-glucose (FDG) PET.

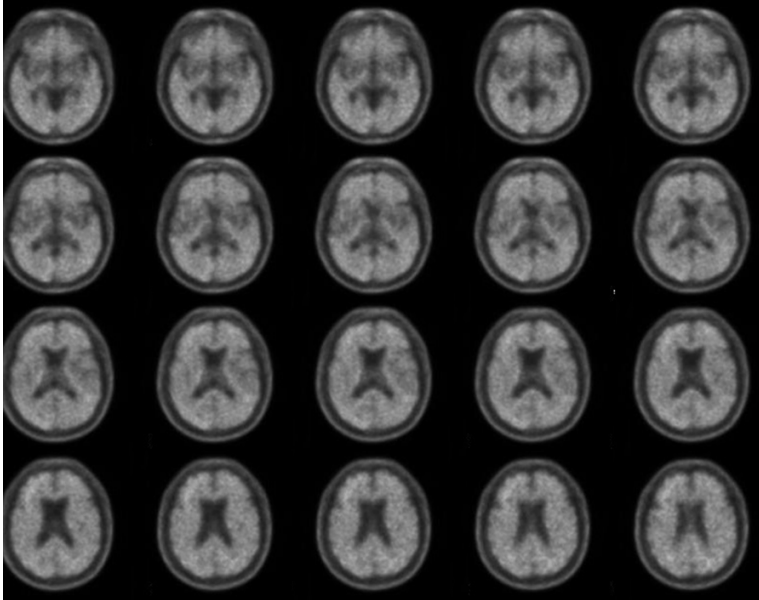
It is worthy of note that by combining information from each of the three biomarker groups, clinicians can also obtain a staging of AD since the more biomarkers are abnormal, the more advanced the pathologic stage is. Another advantage of this classification is its flexibility to incorporate new biomarkers for each category.

In this context molecular imaging with specific probes (i.e. with amyloid or tau radioligands) plays a fundamental role.

#### *The pittsburgh compound B (PIB)*

As the amyloid cascade hypothesis presents a high rate of acceptance by the scientific community, the target for the molecular imaging of AD has been represented by a radioligand binding to the insoluble fibrillar forms of amyloid peptides. The chemical structures of the mentioned radiotracers in the manuscript are reported in **Figure 2**.

$^{11}\text{C}$ -Pittsburgh Compound B (PIB) was the first radioligand developed for PET imaging. It was derived from a fluorescent amyloid dye (i.e. the thioflavin T) and developed at Pittsburgh University. It was found to present high affinity and specificity for fibrillar Abeta-aggregates [11]. The first study in humans with PIB was published in 2004 and included 16 patients with AD and 9 healthy volunteers. Compared with controls, AD patients typically showed marked retention of PIB in areas of association cortex known to contain large amounts of amyloid deposits [13]. Furthermore, Mintun et al. investigated whether abnormal binding of PIB



**Figure 3.** A 65 year-old-male with cognitive impairment. PET with  $^{18}\text{F}$ -florbetaben (axial slices) showed radioligand binding in the cortical regions, indicative of high amyloid burden.

in brain may occur in clinically normal individuals, prior to the development of cognitive changes. It has to be pointed out that PIB-PET was found able to detect amyloid deposits not only in AD patients, but also in some nondemented patients, thus suggesting that amyloid imaging might be sensitive for the detection of preclinical AD [14].

The relationship between PIB uptake and the topography of amyloid plaques at post mortem examination was investigated by Ikonomic et al. [15]. The authors examined 28 clinically diagnosed and autopsy-confirmed Alzheimer's disease subjects, including 1 AD patient who had undergone PIB-PET imaging 10 months prior to death. It was found out a direct correlation of *in vivo* PIB retention with the region-matched quantitative analyses of Abeta plaques in the same patient, thus supporting the validity of PIB-PET as a method for the evaluation of amyloid plaque burden.

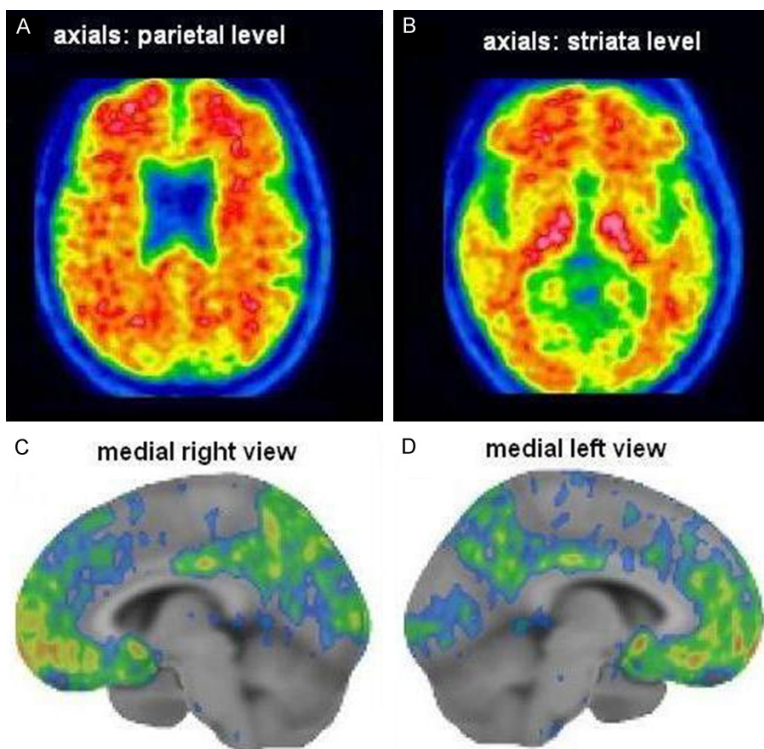
Of note, PIB is labeled with  $^{11}\text{C}$  with a short 20 minutes half-life limiting the use of this radiopharmaceutical only in PET-centers with on-site cyclotron and experience in  $^{11}\text{C}$ -radiochemistry. These drawbacks triggered the development of  $^{18}\text{F}$ -labeled radioligands for the imaging of amyloid deposits in AD.

*The amyloid PET  $^{18}\text{F}$ -labeled radiopharmaceuticals*

**$^{18}\text{F}$ -florbetapir:**  $^{18}\text{F}$ -florbetapir (Amyvid, Eli Lilly/Avid Radiopharmaceuticals), a derivative from stilbene, was the first  $^{18}\text{F}$ -labeled PET tracer developed for the imaging of amyloid plaques with PET technology [16]. It was approved by FDA in 2012. Preclinical studies demonstrated high binding affinity of  $^{18}\text{F}$ -florbetapir to Abeta fibrils and specific labeling of amyloid plaques in the cortical regions and hippocampus. After injection, the tracer diffuses through the blood-brain barrier with kinetics similar to those for PIB but faster than those for other  $^{18}\text{F}$ -labeled amyloid imaging agents. In patients with AD,

$^{18}\text{F}$ -florbetapir showed a clear separation between cortical and cerebellar activity beginning around 30 min after injection, thus allowing starting brain PET scan at 30-50 minutes post injection. In a report from Wong et al. [17],  $^{18}\text{F}$ -florbetapir uptake in brain was visually evaluated and also analyzed by semiquantitative methods that confirmed significant elevations of tracer uptake in several brain regions of AD patients, compared with controls. Furthermore, results from phase III clinical trial showed a strong correlation between  $^{18}\text{F}$ -florbetapir PET images and the distribution of amyloid depositions at post mortem examination. No serious adverse events were reported in any of the clinical trials of  $^{18}\text{F}$ -florbetapir [18].

**$^{18}\text{F}$ -florbetaben:**  $^{18}\text{F}$ -florbetaben (Neuraceq, Piramal Imaging) is an  $^{18}\text{F}$ -labeled derivative from stilbene and was approved by FDA in 2014 [19].  $^{18}\text{F}$ -florbetaben was demonstrated to present nanomolar binding affinity to synthetic beta-amyloid fibrils and AD brain homogenate.  $^{18}\text{F}$ -florbetaben binding to amyloid plaques has been revealed in AD brain sections [20]. Worth of note,  $^{18}\text{F}$ -florbetaben was found not to bind to tau- or alpha-synuclein deposits thus showing high specificity for amyloid neuritic plaques. After injection, the compound binds to plasma proteins and is metabolized by several cyto-



**Figure 4.** A 63 year-old-female patient with amnesic MCI (MMSE = 24/30). Amyloid PET with  $^{18}\text{F}$ -flutemetamol was positive showing tracer accumulation in the cortical regions of interest, as evident in the axial slices at the level of the parietal lobes (A) and of the striata (B). Abnormal radiopharmaceutical accumulation was also detected in the frontal lobe, in the posterior cingulate cortex and in the precuneus at the quantitative analysis performed by the dedicated software *Cortex ID Suite* (GE Healthcare), as shown in the medial right (C) and left (D) volume rendering views.

chrome enzymes. Preliminary studies in animals supported the usefulness of  $^{18}\text{F}$ -florbetaben for the imaging of amyloid plaques as in a mouse over-expressing mutant beta-amyloid precursor protein the concentration of the tracer was found significantly high [21]. In a study comparing  $^{18}\text{F}$ -florbetaben with PIB, both tracers were found equally accurate in discriminating patients with AD from healthy controls with an excellent correlation at the semiquantitative analysis [22]. The recommended activity is 300 MBq, with scan duration of 20 min, starting 90 min after tracer administration. According to the manufacture's indications, PET images should be displayed in the transaxial orientation using gray scale or inverse gray scale (Figure 3).

**$^{18}\text{F}$ -flutemetamol:**  $^{18}\text{F}$ -flutemetamol (GE Healthcare. Vizamyli™) is another compound developed for AD imaging. It is an  $^{18}\text{F}$ -labeled derivative of PIB, approved by FDA in 2013 [23]. It

was developed by General Electric Healthcare and presents similar kinetic properties to those of PIB. Post mortem examination in AD brain homogenates demonstrated a strong correlation between binding of  $^{18}\text{F}$ -flutemetamol and the localization of amyloid deposits in different regions of the brain [24]. The cortical retention of PIB and  $^{18}\text{F}$ -flutemetamol closely matched also in the first report in humans consisting of a dual tracer study in 1 patient affected by AD and in 2 healthy controls [25]. A phase-III trial including 176 patients undergoing PET with  $^{18}\text{F}$ -flutemetamol demonstrated that the compound was safe with high sensitivity and specificity for the *in vivo* detection of brain beta-amyloid plaque density [26, 27]. The recommended activity to be administered is 185 Mbq, the scan duration and the starting time are similar to those reported for  $^{18}\text{F}$ -florbetaben. For  $^{18}\text{F}$ -flutemetamol, all images (axial, coronal, sagittal) should be displayed with a color scale providing progression of low to high intensity (Figure 4).

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**Table 1** summarizes the main manuscripts on the use of  $^{18}\text{F}$ -labeled amyloid radiopharmaceuticals in different clinical settings.

#### *Amyloid-PET imaging in mild cognitive impairment*

Mild Cognitive Impairment (MCI) is a clinical disorder characterized by a moderate impairment of the thinking abilities. MCI is worldwide considered as a "gray zone" between intact cognitive functions and dementia [28]. According to the original classification of the Mayo Clinic [29], to be categorized as having MCI, a patient should present memory complaints in spite of preserved general cognitive functioning, as well as the capability to perform daily life activities independently. MCI is considered a pre-dementia state, as MCI patients present

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**Table 1.** Summary of the main manuscripts on the use of  $^{18}\text{F}$ -labeled amyloid radiopharmaceuticals in clinical setting

References	Year of publication	Type of study	Tracer	Patients	Comment
<i>Amyloid PET for the imaging of MCI</i>					
Doraiswamy et al.	2014	Multi-center	$^{18}\text{F}$ -florbetapir	152	Amyloid-PET scan predicted greater cognitive and global deterioration over a 3-year follow-up
Pontecorvo et al.	2017	Multi-center	$^{18}\text{F}$ -florbetapir	618	PET changed therapeutic management in 68% of patient with MCI possible due to AD
Ong et al.	2013	Single center	$^{18}\text{F}$ -florbetaben	45	Correlation between amyloid burden and cognitive impairment
Ong et al.	2015	Single center	$^{18}\text{F}$ -florbetaben	45	Amyloid-PET predicted conversion from MCI to AD
Thurfjell L et al.	2012	Single center	$^{18}\text{F}$ - $^{18}\text{F}$ -flutemetamol	72	Amyloid-PET predicted conversion from MCI to AD
Duara et al.	2013	Multi-center/phase 2	$^{18}\text{F}$ - $^{18}\text{F}$ -flutemetamol	72	Inverse correlation between the amyloid burden and the hippocampus volume
<i>Amyloid PET for the diagnosis of AD</i>					
Barthel et al.	2011	Single-center/phase 0	$^{18}\text{F}$ -florbetaben	20	Amyloid-PET discriminates AD patients vs healthy controls
Rowe et al.	2008	Single center	$^{18}\text{F}$ -florbetaben	35	Amyloid-PET distinguishes AD from FTD
Kobylecki et al.	2015	Single center	$^{18}\text{F}$ -florbetapir	28	$^{18}\text{F}$ -florbetapir uptake was significantly higher in AD than FTD
Zwan et al.	2012	Multi-center	$^{18}\text{F}$ - $^{18}\text{F}$ -flutemetamol	211	Initial diagnosis was changed on the basis of amyloid-PET
<i>Correlation between FDG and amyloid PET</i>					
Chiaravalloti et al.	2018	Single center	$^{18}\text{F}$ -florbetaben + FDG	38	Combined amyloid and FDG PET shows that amyloid burden in brain is related to cortical dysfunction
Ben Bouallègue et al.	2018	Multi-center	$^{18}\text{F}$ -florbetapir + FDG	684	Correlation between amyloid burden and cortical hypometabolism
<i>Dual phase imaging</i>					
Lin et al.	2016	Single center	$^{18}\text{F}$ -florbetapir	84	Dual phase amyloid-PET detects both perfusion deficit and amyloid accumulation
Kuo et al.	2017	Single center	$^{18}\text{F}$ -florbetaben	22	Dual phase amyloid-PET can be useful to discriminate between progressive primary aphasia and AD

Abbreviations: MCI, mild cognitive impairment; AD, Alzheimer's disease; FTD, frontotemporal dementia.

higher risk of evolving to dementia with about 10% MCI subjects converting to dementia per year.

Amyloid-PET imaging with  $^{18}\text{F}$ -labeled compounds has been applied for predicting the probability of conversion from MCI to AD. A prospective multicenter study [30] involved 69 cognitively normal controls, 52 with recently diagnosed MCI and 31 with probable AD to evaluate whether subjects with amyloid pathology, detected using  $^{18}\text{F}$ -florbetapir PET, presented greater cognitive decline than subjects without amyloid pathology. The authors found that all MCI subjects with positive amyloid-PET scan showed greater cognitive and global deterioration over a 3-year follow-up as compared with subjects with negative amyloid-PET scan. These results were subsequently confirmed in a larger series of 618 patients with MCI possibly due to AD in which a high percentage of subjects (i.e. 68%) received a change in medication on the basis of amyloid-PET results [31].

As concerns the imaging of MCI patients, Ong et al. evaluated 45 MCI patients with PET and  $^{18}\text{F}$ -florbetaben [32]. The authors found high Abeta burden in 53% of MCI subjects. Of note, a quantitative approach was applied to calculate the standardized uptake value ratio (SUVR) in the cortical regions of interest using the cerebellar cortex as reference with a threshold  $\geq 1.45$  to discriminate high from low Abeta burden in the examined subjects. It has to be pointed out that regression analyses showed SUVR and hippocampal volume both contributing to episodic memory impairment in independent fashion, thus suggesting that amyloid accumulation might have a direct effect on memory storage and retrieval. This lack of correlation between SUVR and hippocampal atrophy is of great interest since the association between Abeta burden and memory is thought to be mediated by hippocampal atrophy [33]. The same author subsequently published a research [34] on a cohort of MCI patients ( $n=45$ ) undergoing PET scan with  $^{18}\text{F}$ -florbetaben, MRI and neuropsychological assessment at baseline and at 2-year with an overall clinical follow-up of 4 years. Among these subjects, at baseline 24 showed amyloid deposits at  $^{18}\text{F}$ -florbetaben PET while the remaining 21 were PET negative. Of note, during follow up 18 (i.e. 78%) of the 24 patients with positive PET progressed to AD, while only 2 patients with negative PET

showed progression to AD, yielding a predictive accuracy of 83% for this imaging modality. It is worth noting that at baseline the authors found a strong association between the entity of  $^{18}\text{F}$ -florbetaben uptake and the grade of memory defect, while over the following 2 years became stronger the association between the hippocampal atrophy and the memory defects. On the basis of this evidence, it might be hypothesized that the amyloid deposition might trigger the neurodegenerative process leading to the morphostructural changes in the hippocampal region.

As regards the potential role of PET with  $^{18}\text{F}$ -flutemetamol for predicting the conversion of MCI to AD, this topic was investigated in a cohort of 27 AD patients, 25 healthy volunteers and 20 subjects with MCI, who underwent a 2 year follow-up for monitoring the progression of the disease [35]. The authors found out that, among the examined subjects, 9 patients with MCI were positive at the amyloid PET scan and, within this group, 8 progressed to AD during the follow up, thus suggesting a high predictive value for MCI conversion for this imaging modality. Another interesting investigation about the role of amyloid-PET with  $^{18}\text{F}$ -flutemetamol in MCI was performed by Duara and colleagues [36]. The authors evaluated the additional value of the combination of structural MRI and  $^{18}\text{F}$ -flutemetamol PET for the correct classification of amnesic MCI (aMCI). Among aMCI subjects, 80% of patients showed both amyloid deposits at PET scan and medial temporal atrophy at MRI with inverse correlation between the amyloid burden and the hippocampus volume. Furthermore, it was found that the amyloid load revealed by  $^{18}\text{F}$ -flutemetamol PET in aMCI was correlated with deficit in executive function and that temporal atrophy was primarily correlated with episodic memory performance and category fluency. Thus, the combination of MRI and  $^{18}\text{F}$ -flutemetamol PET was found to be of additive value for the correct clinical classification of aMCI.

### *Amyloid-PET imaging for the diagnosis of Alzheimer's disease*

$^{18}\text{F}$ -labeled amyloid tracers have been widely investigated for assessing their added value for the correct diagnosis of AD. In this regard, Barthel et al. performed a phase 0 study in order to evaluate the capacity of  $^{18}\text{F}$ -florbeta-

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ben in discriminating between AD and healthy controls: 10 patients with mild-moderate probable AD and 10 age-matched healthy controls were enrolled [37]. The subjects underwent PET scan with  $^{18}\text{F}$ -florbetaben and images were assessed by both visual and semiquantitative analysis. The authors found that  $^{18}\text{F}$ -florbetaben presented high accuracy in discriminating AD from healthy controls with good inter-observer agreement both for qualitative and quantitative assessment. Furthermore, amyloid-PET was found to have high accuracy for the differential diagnosis between AD and fronto-temporal dementia (FTD): although in a limited cohort of patients ( $n=35$ ),  $^{18}\text{F}$ -florbetaben uptake in brain measured by the SUVR was significantly higher in AD patients than in those affected by FTD. Of note, this study confirmed visual and quantitative interpretation of the images equally sensitive and specific for the diagnosis of AD [38].

The clinical usefulness for amyloid-PET imaging for distinguishing AD from FTD was confirmed also in studies performed with  $^{18}\text{F}$ -florbetapir and  $^{18}\text{F}$ -flutemetamol. In this regard, it has been published a paper by Kobylecki and collaborators: 10 AD patients, 8 FTD subjects and 10 healthy controls were carefully examined by neuropsychological tests, MRI and genetic analysis of the apolipoprotein E status [39]. All participants underwent PET scans with  $^{18}\text{F}$ -florbetapir and images were assessed by qualitative and quantitative evaluation. This study indicated that  $^{18}\text{F}$ -florbetapir uptake was significantly higher in AD than in FTD patients. It has to be pointed out that 1 patient with FTD but homozygous for apolipoprotein E presented high amyloid burden at PET scan.

Interesting results in this field were obtained in a prospective bi-center study recently published in which 211 patients were included. All subjects were divided in 4 groups according to the expected underlying etiology: 138 were expected to have AD, 28 FTD, 18 other dementia diagnosis and the remaining 12 were considered to present non-neurodegenerative disease. All patients underwent PET scans with  $^{18}\text{F}$ -flutemetamol and, subsequently, initial diagnosis was revised on the basis of PET results. In 59 (28%) patients, the PET findings were inconsistent with expected PET results prior to scanning. In particular, a negative PET scan in patients with an initial diagnosis of AD led to a change in diagnosis in 26 cases while 4

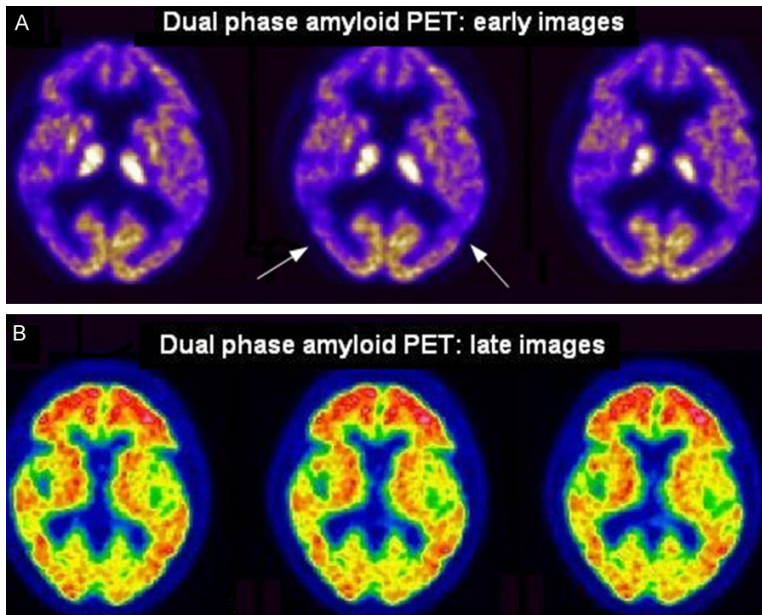
patients with pre-PET diagnosis of FTD had a change in diagnosis to AD due to positive amyloid imaging [40].

### *Correlation between FDG PET and amyloid-PET imaging*

A solid amount of scientific data proved the usefulness of FDG PET for the imaging of metabolic activity in patients with dementia [41, 42]. The typical pattern of FDG uptake in AD patients consists in a regional hypometabolism in the temporo-parietal lobes. However, it has been described an involvement of the frontal cortex when the disease progresses, while other regions of the brain, such as striata and cerebellum are generally preserved [43]. Of note, FDG PET was found to be highly sensitive for the diagnosis of AD, but with low specificity in differentiating AD from other neurodegenerative diseases. Furthermore, it is worth mentioning that FDG PET resulted of great value for predicting patient's outcome: a negative FDG PET in a subject with MCI was found to be indicative of poor probability of progression during the mean 3-year follow-up [44]. As concerns the sensitivity for discriminating AD from healthy controls and other dementias, automated voxel-based analysis may be helpful: in a multi-center study including 548 subjects, this approach was able to correctly identify 95% AD, 92% DLB, 94% FTD, and 94% healthy controls [45].

Since FDG and  $^{18}\text{F}$ -labeled amyloid tracers provide complementary information in patients with cognitive impairment, several papers have investigated the relationship between the metabolic pattern and the distribution of amyloid deposits. In 2015, Frings and colleagues evaluated whether the asymmetric deposition of amyloid burden in brain was correlated with hypometabolism and clinical symptoms: 132 patients were submitted to both FDG and PIB PET [46]. A positive correlation between asymmetries of PIB binding and hypometabolism was detected in 6 of 25 brain regions: most interestingly, the hypometabolism was more pronounced on the side of greater amyloid deposition. These preliminary results were recently confirmed by other investigators with  $^{18}\text{F}$ -labeled amyloid compounds. In particular, a recent paper by Chiaravalloti et al. explored the relationship between FDG and  $^{18}\text{F}$ -florbetaben uptake in 38 patients: SPM analysis in AD patients demonstrated a significant negative





**Figure 5.** A 66-year-old female with cognitive impairment (amnesic MCI, MMSE 22/30). Patient was submitted to dual phase amyloid PET scan with  $^{18}\text{F}$ -flutemetamol. Axial early image (first row, A) showed bilateral perfusion defect in the temporo-parietal regions (white arrows) as typically found in AD patients. Late phase (axial B) was positive for high amyloid burden. This case illustrates the potential usefulness of dual-phase amyloid imaging for the concomitant assessment of both amyloid burden and neuronal dysfunction.

correlation between  $^{18}\text{F}$ -florbetaben and FDG uptake in temporal and parietal lobes bilaterally, thus suggesting that the amyloid burden in AD might be related to the neuronal dysfunction [47]. An even larger cohort of patients ( $n=684$ ) was evaluated in the study published by Ben Bouallègue et al. who performed PET with  $^{18}\text{F}$ -florbetapir and FDG in participants to the Alzheimer's Disease Neuroimaging Initiative (ADNI) [48]. In such subjects, the correlation between regional amyloid and metabolic uptake was evaluated and the predictive value of PET concerning the conversion of MCI to AD was assessed. Of note, among these patients, the rate of five-year conversion was highest in subjects with both positive FDG and amyloid PET. Thus, the complementary assessment of metabolism and amyloid burden seems to be of value for predicting the conversion of MCI to AD.

In this respect, the possibility of acquiring information of neuronal dysfunction and amyloid burden with a single imaging modality would be of great usefulness for the characterization of patients with cognitive impairment. This need triggered the development of the so-

called "dual-phase amyloid imaging" [49]. This approach consists of a first short (5-6 minutes) image acquired, often as dynamic modality, immediately after the injection of the compound followed by a late phase to assess the binding of the tracer to the amyloid deposits (Figure 5). The preliminary published reports indicate that the images obtained in the first phase are very similar to the perfusion data obtained by the single photon emission tomography (SPECT) and to the metabolic pattern revealed by FDG PET [50, 51]. On the contrary, the late phase is able to detect the amyloid accumulation in brain. This dual-time-point approach presents several doubtless advantages: first of all, it allows a reduction of the overall dose delivered to the patient, as compared to the sequential FDG

and amyloid PET imaging. Furthermore, the dual phase imaging may entail lower medical costs and radiopharmaceutical expenses. However, although promising, the dual phase amyloid imaging needs further validation with larger cohorts of patients.

#### *Appropriate use of amyloid-PET imaging and its limitations*

Which is the correct place of the amyloid imaging with PET in the diagnostic workflow of dementia is a still debated issue. In 2013, it has been proposed by Vandenberghe and colleagues [52] that the appropriate use of amyloid-PET should consider the clinical context, the health care system and how AD diagnosis is perceived in the society. In the same year, the society of Nuclear Medicine and Molecular Imaging and the Alzheimer's Association jointly published a document focusing the appropriate use criteria (AUC) for amyloid imaging in clinical practice: 1) patients with persistent or progressive unexplained MCI; 2) patients satisfying core clinical criteria for possible AD because of unclear clinical presentation, either an atypical clinical course or an etiologically mixed presen-

tation; 3) patients with progressive dementia and atypically early age of onset (usually defined as 65 years or less in age) [53]. It is worth mentioning that the clinical impact of amyloid-PET resulted greater when it was clinically used according to the AUC: among 229 subjects with cognitive decline undergoing amyloid imaging, higher rates of change in management plans after scanning were found in patients fulfilling the AUC than in non-AUC cases [54].

Several limitations can be considered for the available  $^{18}\text{F}$ -labeled amyloid tracers. First of all, the clinical approach for the interpretation of an amyloid-PET scan is dichotomic: positive or negative for amyloid burden. This "binary" approach may result problematic in case of ambiguous PET scan. In such patients, the quantitative analysis of tracer binding in the cortical regions of interest may be helpful to gain a correct diagnosis. Furthermore, all  $^{18}\text{F}$ -labeled amyloid PET tracers present consistent non-specific binding to brain white matter that may hinder image interpretation. Of note, it has been demonstrated that cognitively normal individuals may present amyloid deposits detectable with PET. The prevalence of amyloid deposits in healthy individuals has been shown to be age-related, since it rises from 10-15% at 65 years to about 50% at 85 years [55].

Furthermore, it is not fully understood whether or not the 3  $^{18}\text{F}$ -labeled amyloid radiopharmaceuticals are equally specific and sensitive in the differential diagnosis between AD and healthy controls. In this regard, it is worth mentioning that Johnson et al. [56] reviewed the most relevant studies performed with the 3 FDA approved radiopharmaceuticals using statistics model. The authors pointed out that every single tracer was validated through a comparison with PIB. Since all these  $^{18}\text{F}$ -labeled amyloid radioligands showed high correlation with PIB, it is reasonable to hypothesize that the 3  $^{18}\text{F}$ -labeled amyloid radiopharmaceuticals are quite similar to each other. All told, although these molecules are similar, it is unclear whether they are fully interchangeable. Only direct head-to-head comparison between the radioligands within the same patients can be of value to answer this important question.

It is worth mentioning that beyond the  $^{18}\text{F}$ -labeled radiopharmaceuticals specifically covered in the present paper, other new tracers for

PET imaging of amyloid burden have been developed, although still not approved by FDA. Sudaram and colleagues have synthesized a radioligand (i.e.  $^{18}\text{F}$ -7B) showing a binding affinity for AD homogenate similar to that of  $^{18}\text{F}$ -florbetaben. This new radiopharmaceutical showed a substantially higher retention in brain of transgenic mice at microPET imaging as compared to wild type animals [57]. More recently, Hogashi and collaborators investigated the potential usefulness of another tracer (i.e.  $^{18}\text{F}$ -FPYBF-2), which is a benzofuran derivative [58]. In the first study in humans, 61 healthy volunteers and 55 patients with suspected dementia were submitted to PET with  $^{18}\text{F}$ -FPYBF-2; among them, 16 subjects also underwent PET with PIB for comparative purpose. The authors found pathological  $^{18}\text{F}$ -FPYBF-2 uptake in patients with AD with a good correlation between the results of this new tracer and those found with PIB. Further studies are needed to better define how much these new amyloid tracers will be helpful to supplement the diagnostic arsenal for the imaging of AD.

Finally, it has to be underlined that amyloid plaques are not the only pathological hallmark of AD. New radiopharmaceuticals specifically addressing other potential surrogate "AD markers" such as the pathological tau proteins are under evaluation to better understand whether these alternative PET probes may be useful for diagnosis and staging of AD [59].

### *Ethical considerations*

The possibility of detecting *in vivo* amyloid deposits with PET technology raises important ethical questions. The amyloid pathological "cascade", underlying the cognitive impairment and the neurodegenerative process, begins many years before the symptomatology is evident. In other words,  $^{18}\text{F}$ -labeled amyloid radiopharmaceuticals might be clinically used also to disclose AD in the preclinical stage. However, the concept of the "pre-clinical AD" is based on the postulation that all subjects with amyloid deposits in brain will develop symptomatic AD during their life. But this postulation is not true: autopsy demonstrated that one-third of the older adults die with cerebral amyloid depositions without expressing a dementia syndrome [60]. Therefore, whether or not to disclose the results of amyloid-PET imaging to cognitive normal individuals, it is a very debated argument

[61]. In this respect, Grill et al. [62] analyzed the pros and cons of disclosing this information to patients, taking into account the principle of *non nocere*. As the authors correctly state in their paper, there are several arguments against the disclosure: first of all, the pre-clinical significance of amyloid-PET is still to be fully defined, since some subjects with amyloid deposits may present unknown protective factors preventing the development of dementia. Secondly, the psychological implications of the disclosure on the life of patients and their relatives have not been adequately investigated. All told, the scientific community should respect the choice of cognitively intact subjects and their rights of being disclosed about their amyloid status, also to make changes in their style of life to prevent or slowing the arise of symptoms. In a recently published paper, it has been demonstrated that the disclosure of amyloid status in a group of cognitively normal subjects did not cause relevant mood disturbance than negative results in a short period of time [63].

### Conclusions

Although the molecular etiopathogenesis of AD is complex and involves several mechanisms, the amyloid accumulation in brain plays a crucial role in triggering the neurodegenerative process. The introduction of three  $^{18}\text{F}$ -labeled radiopharmaceuticals (i.e.  $^{18}\text{F}$ -florbetapir,  $^{18}\text{F}$ -florbetaben and  $^{18}\text{F}$ -flutemetamol) has opened intriguing and unique possibilities for the *in vivo* imaging of amyloid deposits. PET with  $^{18}\text{F}$ -labeled amyloid tracers has been shown accurate for discriminating AD from healthy controls and other forms of dementia. Furthermore, this innovative imaging modality has been demonstrated of predictive value for defining the risk of conversion of MCI to AD. The "dual phase amyloid PET" seems to be promising for obtaining information on the neuronal dysfunction and the amyloid status with a single imaging modality. Further studies with larger sample size are needed to better define the limitations of amyloid-PET and whether or not these three  $^{18}\text{F}$ -labeled compounds are fully interchangeable.

### Disclosure of conflict of interest

None.

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### References

- [1] Adlard PA, Tran BA, Finkelstein DI, Desmond PM, Johnston LA, Bush AI, Egan GF. A review of  $\beta$ -amyloid neuroimaging in Alzheimer's disease. *Front Neurosci* 2014; 8: 327.
- [2] Minati L, Edginton T, Bruzzone MG, Giaccone G. Current concepts in Alzheimer's disease: a multidisciplinary review. *Am J Alzheimers Dis Other Demen* 2009; 24: 95-121.
- [3] Johnson KA, Fox NC, Sperling RA, Klunk WE. Brain imaging in Alzheimer disease. *Cold Spring Harb Perspect Med* 2012; 4: a006213.
- [4] Gaugler JE, Ascher-Svanum H, Roth DL, Fafo-wora T, Siderowf A, Beach TG. Characteristics of patients misdiagnosed with Alzheimer's disease and their medication use: an analysis of the NACC-UDS database. *BMC Geriatrics* 2013; 13: 137.
- [5] Murphy MP, LeVine H. Alzheimer's disease and the  $\beta$ -Amyloid peptide. *J Alzheimers Dis* 2010; 19: 311.
- [6] Sanabria-Castro A, Alvarado-Echeverría I, Mönge-Bonilla C. Molecular pathogenesis of Alzheimer's disease: an update. *Ann Neurosci* 2017; 24: 46-54.
- [7] Hu WT, Watts KD, Shaw LM, Howell JC, Trojanowski JQ, Basra S, Glass JD, Lah JJ, Levey AI. CSF beta-amyloid 1-42-what are we measuring in Alzheimer's disease? *Ann Clin Transl Neurol* 2015; 2: 131-139.
- [8] Zhang X, Li Y, Xu H, Zhang Y. The  $\gamma$ -secretase complex: from structure to function. *Front Cell Neurosci* 2014; 8: 427.
- [9] Gu L, Guo Z. Alzheimer's A $\beta$ 42 and A $\beta$ 40 peptides form interlaced amyloid fibrils. *J Neurochem* 2013; 126: 305-311.
- [10] Kaye R, Lasagna-Reeves CA. Molecular mechanisms of amyloid oligomers toxicity. *J Alzheimers Dis* 2013; 33: S67-78.
- [11] Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, Holtzman DM, Jagust W, Jessen F, Karlawish J, Liu E, Molinuevo JL, Montine T, Phelps C, Rankin KP, Rowe CC, Scheltens P, Siemers E, Snyder HM, Sperling R; Contributors. Toward a biological definition of Alzheimer's disease. *Alzheimers Dement* 2018; 14: 535-562.
- [12] Mathis CA, Wang Y, Holt DP, Huang GF, Debnath ML, Klunk WE. Synthesis and evaluation of  $^{11}\text{C}$ -labeled 6-substituted 2-arylbenzothiazoles as amyloid imaging agents. *J Med Chem* 2003; 46: 2740-2754.
- [13] Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, Bergström M, Savitcheva I, Huang GF, Estrada S, Ausén B, Debnath ML,

## Amyloid neuroimaging in Alzheimer's disease

- Barletta J, Price JC, Sandell J, Lopresti BJ, Wall A, Koivisto P, Antoni G, Mathis CA, Långström B. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. *Ann Neurol* 2004; 55: 306-319.
- [14] Mintun MA, Larossa GN, Sheline YI, Dence CS, Lee SY, Mach RH, Klunk WE, Mathis CA, DeKosky ST, Morris JC. [<sup>11</sup>C]PIB in a nondemented population: potential antecedent marker of Alzheimer disease. *Neurology* 2006; 67: 446-452.
- [15] Ikonomic MD, Klunk WE, Abrahamson EE, Mathis CA, Price JC, Tsopelas ND, Lopresti BJ, Ziolk S, Bi W, Paljug WR, Debnath ML, Hope CE, Isanski BA, Hamilton RL, DeKosky ST. Post-mortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. *Brain* 2008; 131: 1630-1645.
- [16] <http://www.amyvid.com/Pages/index.aspx>.
- [17] Wong DF, Rosenberg PB, Zhou Y, Kumar A, Raymond V, Ravert HT, Dannals RF, Nandi A, Brasić JR, Ye W, Hilton J, Lyketsos C, Kung HF, Joshi AD, Skovronsky DM, Pontecorvo MJ. In vivo imaging of amyloid deposition in Alzheimer disease using the radioligand <sup>18</sup>F-AV-45 (florbetapir F 18). *J Nucl Med* 2010; 51: 913-920.
- [18] Okamura N, Yanai K. <sup>18</sup>F-florbetapir (18F), a PET imaging agent that binds to amyloid plaques for the potential detection of Alzheimer's disease. *Drugs* 2010; 13: 890-899.
- [19] <http://piramal.com/neuraceq/>.
- [20] Sabri O, Seibyl J, Rowe C, Barthel H. Beta-amyloid imaging with florbetaben. *Clin Transl Imaging* 2015; 3: 13-26.
- [21] Rominger A, Brendel M, Burgold S, Keppler K, Baumann K, Xiong G, Mille E, Gildehaus FJ, Carlsen J, Schlichtiger J, Niedermoser S, Wängler B, Cumming P, Steiner H, Herms J, Haass C, Bartenstein P. Longitudinal assessment of cerebral beta-amyloid deposition in mice over-expressing Swedish mutant beta-amyloid precursor protein using <sup>18</sup>F-florbetaben PET. *J Nucl Med* 2013; 54: 1127-1134.
- [22] Villemagne VL, Mulligan RS, Pejoska S, Ong K, Jones G, O'Keefe G, Chan JG, Young K, Tochon-Danguy H, Masters CL, Rowe CC. Comparison of <sup>11</sup>C-PiB and <sup>18</sup>F-florbetaben for Aβ imaging in ageing and Alzheimer's disease. *Eur J Nucl Med Mol Imaging* 2012; 39: 983-989.
- [23] [http://www.3ghealthcare.com/en/Products/Categories/Nuclear\\_Imaging\\_Agents/Vizamyl](http://www.3ghealthcare.com/en/Products/Categories/Nuclear_Imaging_Agents/Vizamyl).
- [24] Mathis CA, Ikonomic MD, Debnath ML, Hamilton RL, DeKosky ST, Klunk WE. Comparison of the binding of 3'-F-PiB and PiB in human brain homogenates. *Neuroimage* 2008; 41 Suppl: T113-4.
- [25] Mathis C, Lopresti B, Mason N, Price J, Flatt N, Bi W. Comparison of the amyloid imaging agents [<sup>18</sup>F]3'-F-PIB and [<sup>11</sup>C]PIB in Alzheimer's disease and control subjects. *J Nucl Med* 2007; 48: 56P.
- [26] Curtis C, Gamez JE, Singh U, Sadowsky CH, Villena T, Sabbagh MN, Beach TG, Duara R, Fleisher AS, Frey KA, Walker Z, Hunjan A, Holmes C, Escovar YM, Vera CX, Agronin ME, Ross J, Bozoki A, Akinola M, Shi J, Vandenberghe R, Ikonomic MD, Sherwin PF, Grachev ID, Farrar G, Smith AP, Buckley CJ, McLain R, Salloway S. Phase 3 trial of <sup>18</sup>F-18F-flutemetamol labeled with radioactive fluorine 18 imaging and neuritic plaque density. *JAMA Neurol* 2015; 72: 287-294.
- [27] Rabinovici GD. The translational journey of brain β-amyloid imaging: from positron emission tomography to autopsy to clinic. *JAMA Neurol* 2015; 72: 265-266.
- [28] Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. *J Intern Med* 2014; 275: 214-228.
- [29] Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Mild cognitive impairment: clinical characterization and outcome. *Arch Neurol* 1999; 56: 303-308.
- [30] Doraiswamy PM, Sperling RA, Johnson K, Reiman EM, Wong TZ, Sabbagh MN, Sadowsky CH, Fleisher AS, Carpenter A, Joshi AD, Lu M, Grundman M, Mintun MA, Skovronsky DM, Pontecorvo MJ; AV45-A11 Study Group. <sup>18</sup>F-florbetapir F 18 amyloid PET and 36-month cognitive decline: a prospective multicenter study. *Mol Psychiatry* 2014; 19: 1044-1051.
- [31] Siderowf A, Dubois B, Doraiswamy PM, Frisoni GB, Grundman M, Nobili F, Sadowsky CH, Salloway S, Arora AK, Chevrette A, Deberdt W, Dell'Agnello G, Flitter M, Galante N, Lowrey MJ, Lu M, McGeehan A, Devous MD Sr, Mintun MA. Effectiveness of <sup>18</sup>F-florbetapir PET imaging in changing patient management. *Dement Geriatr Cogn Disord* 2017; 44: 129-143.
- [32] Ong K, Villemagne VL, Bahar-Fuchs A, Lamb F, Chételat G, Raniga P, Mulligan RS, Salvado O, Putz B, Roth K, Masters CL, Reininger CB, Rowe CC. <sup>18</sup>F-florbetaben Aβ imaging in mild cognitive impairment. *Alzheimers Res Ther* 2013; 5: 4.
- [33] Mormino EC, Kluth JT, Madison CM, Rabinovici GD, Baker SL, Miller BL, Koeppe RA, Mathis CA, Weiner MW, Jagust WJ. Episodic memory loss is related to hippocampal-mediated beta-amyloid deposition in elderly subjects. *Brain* 2009; 132: 1310-1323.
- [34] Ong KT, Villemagne VL, Bahar-Fuchs A, Lamb F, Langdon N, Catafau AM, Stephens AW, Seibyl J, Dinkelborg LM, Reininger CB, Putz B, Rohde B, Masters CL, Rowe CC. Aβ imaging with <sup>18</sup>F-

## Amyloid neuroimaging in Alzheimer's disease

- florbetaben in prodromal Alzheimer's disease: a prospective outcome study. *J Neurol Neurosurg Psychiatry* 2015; 86: 431-436.
- [35] Thurfjell L, Lötjönen J, Lundqvist R, Koikkalainen J, Soininen H, Waldemar G, Brooks DJ, Vandenberghe R. Combination of biomarkers: PET [18F]18F-18F-flutemetamol imaging and structural MRI in dementia and mild cognitive impairment. *Neurodegener Dis* 2012; 10: 246-249.
- [36] Duara R, Loewenstein DA, Shen Q, Barker W, Potter E, Varon D, Heurlin K, Vandenberghe R, Buckley C. Amyloid positron emission tomography with <sup>18</sup>F-flutemetamol and structural magnetic resonance imaging in the classification of mild cognitive impairment and Alzheimer's. *Alzheimers Dement* 2013; 9: 295-301.
- [37] Barthel H, Luthardt J, Becker G, Patt M, Hammerstein E, Hartwig K, Eggers B, Sattler B, Schildan A, Hesse S, Meyer PM, Wolf H, Zimmermann T, Reischl J, Rohde B, Gertz HJ, Reininger C, Sabri O. Individualized quantification of brain  $\beta$ -amyloid burden: results of a proof of mechanism phase 0 <sup>18</sup>F-florbetaben PET trial in patients with Alzheimer's disease and healthy controls. *Eur J Nucl Med Mol Imaging* 2011; 38: 1702-1714.
- [38] Rowe CC, Ackerman U, Browne W, Mulligan R, Pike KL, O'Keefe G, Tochon-Danguy H, Chan G, Berlangieri SU, Jones G, Dickinson-Rowe KL, Kung HP, Zhang W, Kung MP, Skovronsky D, Dyrks T, Holl G, Krause S, Friebe M, Lehman L, Lindemann S, Dinkelborg LM, Masters CL, Villemagne VL. Imaging of amyloid beta in Alzheimer's disease with <sup>18</sup>F-BAY94-9172, a novel PET tracer: proof of mechanism. *Lancet Neurol* 2008; 7: 129-135.
- [39] Kobylecki C, Langheinrich T, Hinz R, Vardy ER, Brown G, Martino ME, Haense C, Richardson AM, Gerhard A, Anton-Rodriguez JM, Snowden JS, Neary D, Pontecorvo MJ, Herholz K. <sup>18</sup>F-florbetapir PET in patients with frontotemporal dementia and Alzheimer disease. *J Nucl Med* 2015; 56: 386-391.
- [40] Zwan MD, Bouwman FH, Konijnenberg E, van der Flier WM, Lammertsma AA, Verhey FR, Aalten P, van Berckel BN, Scheltens P. Diagnostic impact of [18F]18F-18F-flutemetamol PET in early-onset dementia. *Alzheimers Res Ther* 2017; 9: 2.
- [41] Shivamurthy VK, Tahari AK, Marcus C, Subramaniam RM. Brain FDG PET and the diagnosis of dementia. *AJR Am J Roentgenol* 2015; 204: W76-85.
- [42] O'Brien JT, Firbank MJ, Davison C, Barnett N, Bamford C, Donaldson C, Olsen K, Herholz K, Williams D, Lloyd J. 18F-FDG PET and perfusion SPECT in the diagnosis of Alzheimer and Lewy body dementias. *J Nucl Med* 2014; 55: 1959-1965.
- [43] Mosconi L. Brain glucose metabolism in the early and specific diagnosis of Alzheimer's disease. *Eur J Nucl Med* 2005; 32: 486-510.
- [44] Silverman DH, Small GW, Chang CY, Lu CS, Kung De Aburto MA, Chen W, Czernin J, Rapoport SI, Pietrini P, Alexander GE, Schapiro MB, Jagust WJ, Hoffman JM, Welsh-Bohmer KA, Alavi A, Clark CM, Salmon E, de Leon MJ, Mielke R, Cummings JL, Kowell AP, Gambhir SS, Hoh CK, Phelps ME. Positron emission tomography in evaluation of dementia: regional brain metabolism and long-term outcome. *JAMA* 2001; 286: 2120-2127.
- [45] Mosconi L, Tsui WH, Herholz K, Pupi A, Drzezga A, Lucignani G, Reiman EM, Holthoff V, Kalbe E, Sorbi S, Diehl-Schmid J, Pernecky R, Clerici F, Caselli R, Beuthien-Baumann B, Kurz A, Minoshima S, de Leon MJ. Multi-center standardized FDG-PET diagnosis of mild cognitive impairment, Alzheimer's disease and other dementias. *J Nucl Med* 2008; 49: 390-398.
- [46] Frings L, Hellwig S, Spehl TS, Bormann T, Buchert R, Vach W, Minkova L, Heimbach B, Klöppel S, Meyer PT. Asymmetries of amyloid- $\beta$  burden and neuronal dysfunction are positively correlated in Alzheimer's disease. *Brain* 2015; 138: 3089-3099.
- [47] Chiaravalloti A, Castellano AE, Ricci M, Barbagallo G, Sannino P, Ursini F, Karalis G, Schilacci O. Coupled imaging with [<sup>18</sup>F]FBB and [<sup>18</sup>F]FDG in AD subjects show a selective association between amyloid burden and cortical dysfunction in the brain. *Mol Imaging Biol* 2018; 20: 659-666.
- [48] Ben Bouallègue F, Mariano-Goulart D, Payoux P; Alzheimer's Disease Neuroimaging Initiative (ADNI). Joint assessment of quantitative <sup>18</sup>F-florbetapir and 18F-FDG regional uptake using baseline data from the ADNI. *J Alzheimers Dis* 2018; 62: 399-408.
- [49] Garibotto V, Morbelli S, Pagani M. Erratum to: dual-phase amyloid PET: hitting two birds with one stone. *Eur J Nucl Med Mol Imaging* 2016; 43: 1747.
- [50] Lin KJ, Hsiao IT, Hsu JL, Huang CC, Huang KL, Hsieh CJ, Wey SP, Yen TC. Imaging characteristic of dual-phase (18)F-18F-florbetapir (AV-45/ Amyvid) PET for the concomitant detection of perfusion deficits and beta-amyloid deposition in Alzheimer's disease and mild cognitive impairment. *Eur J Nucl Med Mol Imaging* 2016; 43: 1304-1314.
- [51] Kuo HC, Hsiao IT, Hsieh CJ, Huang CY, Huang KL, Wai YY, Chuang WL, Kung MP, Chu YC, Yen TC, Lin KJ, Huang CC. Dual-phase <sup>18</sup>F-florbetapir positron emission tomography in patients with primary progressive aphasia, Alzheimer's disease, and healthy controls: a preliminary study. *J Formos Med Assoc* 2017; 116: 964-972.

## Amyloid neuroimaging in Alzheimer's disease

- [52] Vandenberghe R, Adamczuk K, Dupont P, Laere KV, Chételat G. Amyloid PET in clinical practice: its place in the multidimensional space of Alzheimer's disease. *Neuroimage Clin* 2013; 2: 497-511.
- [53] Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P, Karlawish JH, Rowe CC, Carrillo MC, Hartley DM, Hedrick S, Pappas V, Thies WH. 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. *J Nucl Med* 2013; 54: 476-490.
- [54] Grundman M, Johnson KA, Lu M, Siderowf A, Dell'Agnello G, Arora AK, Skovronsky DM, Mintun MA, Pontecorvo MJ; <sup>18</sup>F-AV-45-A17 Study Group. Effect of amyloid imaging on the diagnosis and management of patients with cognitive decline: impact of appropriate use criteria. *Dement Geriatr Cogn Disord* 2016; 41: 80-92.
- [55] Rowe CC, Ellis KA, Rimajova M, Bourgeat P, Pike KE, Jones G, Fripp J, Tochon-Danguy H, Morandau L, O'Keefe G, Price R, Raniga P, Robins P, Acosta O, Lenzo N, Szoek C, Salvado O, Head R, Martins R, Masters CL, Ames D, Villemagne VL. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. *Neurobiol Aging* 2010; 31: 1275-1283.
- [56] Johnson, KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P, Karlawish JH, Rowe CC, Carrillo MC, Hartley DM, Hedrick S, Pappas V, Thies WH; Alzheimer's Association; Society of Nuclear Medicine and Molecular Imaging; Amyloid Imaging Taskforce (2013). Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force (AIT), the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the Alzheimer Association (AA). *Alzheimers Dement* 2013; 9: e1-e16.
- [57] Sundaram GS, Dhavale D, Prior JL, Sivapackiam J, Laforest R, Kotzbauer P, Sharma V. Synthesis, characterization, and preclinical validation of a PET radiopharmaceutical for interrogating A $\beta$  ( $\beta$ -amyloid) plaques in Alzheimer's disease. *EJNMMI Res* 2015; 5: 33.
- [58] Higashi T, Nishii R, Kagawa S, Kishibe Y, Takahashi M, Okina T, Suzuki N, Hasegawa H, Nagahama Y, Ishizu K, Oishi N, Kimura H, Watanabe H, Ono M, Saji H, Yamauchi H. <sup>18</sup>F-FPYBF-2, a new F-18-labelled amyloid imaging PET tracer: first experience in 61 volunteers and 55 patients with dementia. *Ann Nucl Med* 2018; 32: 206-216.
- [59] James OG, Doraiswamy PM, Borges-Neto S. PET imaging of tau pathology in Alzheimer's disease and tauopathies. *Front Neurol* 2015; 6: 38.
- [60] Vlassenko AG, Benzinger TL, Morris JC. PET amyloid-beta imaging in preclinical Alzheimer's disease. *Biochim Biophys Acta* 2012; 1822: 370-379.
- [61] Bennett DA, Schneider JA, Arvanitakis Z, Kelly JF, Aggarwal NT, Shah RC, Wilson RS. Neuropathology of older persons without cognitive impairment from two community-based studies. *Neurology* 2006; 66: 1837-1844.
- [62] Grill JD, Johnson DK, Burns JM. Should we disclose amyloid imaging results to cognitively normal individuals? *Neurodegener Dis Manag* 2013; 3: 43-51.
- [63] Wake T, Tabuchi H, Funaki K, Ito D, Yamagata B, Yoshizaki T, Kameyama M, Nakahara T, Murakami K, Jinzaki M, Mimura M. The psychological impact of disclosing amyloid status to Japanese elderly: a preliminary study on asymptomatic patients with subjective cognitive decline. *Int Psychogeriatr* 2017; 2: 1-5.