Continuing education

Molecular neuroimaging in degenerative dementias

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A B S T R A C T

In the context of the limitations of structural imaging, brain perfusion and metabolism using SPECT and PET have provided relevant information for the study of cognitive decline. The introduction of the radiotracers for cerebral amyloid imaging has changed the diagnostic strategy regarding Alzheimer’s disease, which is currently considered to be a "continuum." According to this new paradigm, the increasing amyloid load would be associated to the preclinical phase and mild cognitive impairment. It has been possible to observe “in vivo” images using 11C-PiB and PET scans.

The characteristics of the 11C-PiB image include specific high brain cortical area retention in the positive cases with typical distribution pattern and no retention in the negative cases. This, in combination with 18F-FDG PET, is the basis of molecular neuroimaging as a biomarker. At present, its prognostic value is being evaluated in longitudinal studies. 11C-PiB-PET has become the reference radiotracer to evaluate the presence of cerebral amyloid. However, its availability is limited due to the need for a nearby cyclotron. Therefore, 18F labeled radiotracers are being introduced. Our experience in the last two years with 11C-PiB, first in the research phase and then as being clinically applied, has shown the utility of the technique in the clinical field, either alone or in combination with FDG. Thus, amyloid image is a useful tool for the differential diagnosis of dementia and it is a potentially useful method for early diagnosis and evaluation of future treatments.

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La neuroimagen molecular en las demencias degenerativas

R E S U M E N

En el contexto de las limitaciones de la imagen estructural, los estudios de perfusión y metabolismo cerebral con SPECT y PET han aportado información relevante en el estudio del deterioro cognitivo. La introducción de radiotrazadores de amiloide cerebral ha replanteado la estrategia diagnóstica en torno a la enfermedad de Alzheimer (EA), considerada actualmente un “continuum”. En este nuevo paradigma, la carga amiloide creciente se asocia al estadio preclínico y de deterioro cognitivo leve de la enfermedad y ha podido ser objetivada en exploraciones “in vivo” gracias a la introducción del 11C-PiB y los tomógrafos PET.

Las características de la imagen 11C-PiB son una elevada retención específica cortical cerebral en los casos positivos, con distribución topográfica característica y no retención en los negativos. Junto al PET con 18F-FDG constituye la base de la neuroimagen molecular como biomarcador y se está valorando su significado pronóstico en estudios longitudinales. El PET con 11C-PiB se ha consolidado como la técnica óptima para valorar la presencia de amiloide cerebral, pero la necesidad de un ciclotrón cercano para su síntesis limita su disponibilidad, por lo que se están introduciendo trazadores análogos marcados con 18F.

Nuestra experiencia en los dos últimos años aplicando el 11C-PiB, primero en fase investigadora y después en la clínica, ha constatado la utilidad de la técnica en el campo asistencial, tanto de forma aislada como en combinación con la FDG. Así pues, la imagen de amiloide ha demostrado ser una herramienta útil en el diagnóstico diferencial de la demencia y un método prometedor de diagnóstico precoz y evaluación de tratamientos futuros.

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Functional imaging in the context of neurodegenerative dementias. Role of molecular imaging

The increase in life expectancy has converted cognitive impairment into a world health care problem of great magnitude and the forecast of the WHO indicates that it will be even greater in the next decades.1 It has been estimated that around the year 2050, one out of every 5 persons will be over the age of 60 years and if, at present, 24 million people have dementia, this figure will double in 2040, with Alzheimer’s disease (AD) being the most prevalent cause.2,3

In the pictures of dementia, the definitive etiologic diagnosis can only be made post-mortem. However, neuroimaging is useful to perform a differential diagnosis in life, providing a more specific representation of the neuropathological substrate than the clinical manifestations which, in these processes, show marked interindividual variability.4,5

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Neuroimaging techniques have received a decisive boost with the incorporation of computed tomography, initially developed for emission tomography (SPECT) but routinely applied in transmission tomography (CT). The classical structural imaging studies have demonstrated a great capacity to detect expansive cerebral lesions or those of another type which may manifest with signs of cognitive impairment, but their diagnostic utility in neurodegenerative dementias is scarce because the alterations revealed are late and little specific.

Ideally, a specific diagnosis would be desirable when the disease load or its extension are still insufficient to cause significant impairment and the treatments could contain the progression or prevent an irreversible deficit. Functional metabolic neuroimaging was developed with the premise that functional changes precede structural alterations, joining the tomographic development (SPECT and positron emission tomography [PET]) with the introduction of the cerebral flow and metabolism radiotracers. 6–9

Cerebral perfusion studies with 99mTc-HMPAO and 99mTc-ECD are able to identify the alterations associated with neurodegenerative dementias earlier, with characteristics patterns of high positive predictive value and help to establish a more certain differential diagnosis between these processes and dementias of vascular or multiinfarction origin (Table 1 and Fig. 1). In the same sense, in virtue of the functional flow metabolism connection, PET studies with 18F-FDG provide better diagnostic results due to the greater spatial resolution of the PET tomographs and the more physiological character of labeled glucose used as a radiotracer (Table 2 and Fig. 2). However, despite their extraordinary value, both techniques share a common limitation: their unspecificity in relation to the etiology of the neurodegenerative process. They reflect a deficit in function but do not make a “positive” diagnosis of the disease. 10

In parallel, albeit with a different foundation, nuclear magnetic resonance (MR) has also followed a spectacular route, providing very valuable structural and volumetric information. In addition, based on these structural principles, diagnostic approaches of cerebral function (fMR) have been developed. Both, MR and functional metabolic neuroimaging involve powerful informatic developments for performing estimations related to topography and quantitative variables with relevant projection in investigation and clinical care. Fusion and multimodality PET/CT and PET/MR are now available, combining both types of information. All of this, together with neurotransmission molecular imaging studies, allow the characterization and management of a good number of these processes. 11

It is now known that the common base of many neurodegenerative processes is the pathological accumulation of different peptides or proteins, such as β-amyloid in AD. These deposits may originate a cascade of alterations in neurotransmission, activation of inflammatory mechanisms, neuronal death and atrophy of cerebral tissue. 12,13 One of the principal problems of the diagnostic criteria based exclusively on clinical manifestations is that when the patient has these manifestations to establish the diagnosis of dementia, the disease responsible is already very extensive. These considerations, together with other advances in neuroscience, have led to a change in paradigm based on the concept of biomarkers, considering dementia as the final state of impairment of the “cognitive continuum”. 14

### Molecular neuroimaging as a biomarker. A new paradigm of Alzheimer’s disease

A biomarker is defined as a characteristic which may be objectively measured and evaluated as an indicator of a normal biological or pathological process or of response to a pharmacologic intervention. The identification of biomarkers is the new context in which the study of these diseases is moving, and in this sense, neuroimaging is considered one of them. Molecular neuroimaging studies the mechanisms implicated in the neurodegenerative process in vivo, allowing an early diagnosis in daily clinical care, differential diagnosis, prognostic evaluation and monitoring of the effect of the therapies used as well as the study and assessment of new therapies. 15

In July 2011, the National Institute on Aging (NIA)-Alzheimer’s Association published guidelines differentiating the dementia of Alzheimer (DA) from the changes preceding or accompanying this disease which, in general, is known as AD. 16–19 In view of the new data, especially provided by the contribution of C-PIB, the need for better defining the dementia associated with AD was emphasized, distinguishing it from other dementias and indicating the need to incorporate new knowledge on the progression of this disease.

#### Table 1
Differential diagnosis of dementias with perfusion tracers (SPECT) and metabolism (18F-FDG-PET).

<table>
<thead>
<tr>
<th>Dementia Type</th>
<th>PET Tracer</th>
<th>Structural and Volumetric Information</th>
<th>Functional Changes</th>
<th>Heterogeneity</th>
<th>Differentiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer disease</td>
<td>18F-FDG</td>
<td>Involvement in parietal, temporal and posterior cingulate areas.</td>
<td>Involvement in parietal, temporal and posterior cingulate areas.</td>
<td>Early phases, asymmetric deficit</td>
<td>Involvement in parietal, temporal and posterior cingulate areas.</td>
</tr>
<tr>
<td>Vascular dementia</td>
<td>Tc-HMPAO</td>
<td>Cortical, subcortical and cerebellar hypoperfusion and hypometabolism in multiple foci</td>
<td>Eroded periventricular white matter</td>
<td>Tumor and inflammatory processes</td>
<td>Involvement in parietal, temporal and posterior cingulate areas.</td>
</tr>
<tr>
<td>Frontal–temporal dementia</td>
<td>Tc-ECD</td>
<td>Involvement of frontal and anterior–medial temporal cortex</td>
<td>Involvement of frontal and anterior–medial temporal cortex</td>
<td>Preservation of sensory motor and visual cortex</td>
<td>Involvement in parietal, temporal and posterior cingulate areas.</td>
</tr>
<tr>
<td>Dementia associated with Parkinson disease</td>
<td>F-FDG</td>
<td>Similar to AD but more preserved temporal–mesial cortex and less visual–occipital</td>
<td>Similar to AD but more preserved temporal–mesial cortex and less visual–occipital</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lewy body dementia</td>
<td></td>
<td>Similar to AD but less preserved occipital and cerebellum</td>
<td>Similar to AD but less preserved occipital and cerebellum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


#### Table 2
Comparison of perfusion SPECT/18F-FDG PET.

- The radiotracers and equipment differ but the principles of interpretation and the underlying neurobiological processes are similar.
- Differences:
  - More detailed spatial resolution of SPECT images (12 mm) compared with PET (6–8 mm).
  - Sometimes in cerebrovascular disease there is a loss of flow metabolism coupling.
  - In general, the magnitude of hypometabolism observed in PET is greater than that of hypoperfusion assessed in SPECT.
- Similar results but less sensitivity and diagnostic precision for SPECT.
- PET adds approximately 15% of diagnostic precision in AD.
- The greater sensitivity of PET is especially relevant to identify the presence of AD in the early stages (Incipient Cognitive Impairment) when the neurodegeneration is less and treatment may be administered.
Fig. 1. Different patterns of cerebral perfusion obtained by SPECT with $^{99m}$Tc-HMPAO in patients with vascular dementia (upper row), Pick dementia (middle row) and AD (bottom row).

Fig. 2. Patient with dementia due to Alzheimer’s disease. The upper row shows transversal slices of a perfusion SPECT performed in this patient with $^{99m}$Tc-ECD and the bottom row shows a PET study with $^{18}$F-FDG in the same patient.

The new guidelines are based more on anatomopathological than clinical criteria and reflect the current comprehension of the molecular mechanisms of AD. The criteria of DA have remained unchanged since 1984, and the new guidelines represent a redefinition of AD, introducing the concept of biomarkers and emphasizing the importance of comorbidity in elderly patients. The guidelines, for which a periodic updating is foreseen, consider AD as a “continuum” in which 3 phases may be distinguished. Each phase of the disease is characterized by a nucleus of clinical criteria (mild cognitive impairment [MCI] and dementia), and the probability that this cognitive impairment is due to AD is qualified by a group of biomarkers. They also recommend that genetic risk and chemical and neuroimaging biomarkers be used in the field of investigation to complete the post-mortem neuropathological data.
The biomarkers proposed for AD are divided into:

1. Biomarkers of accumulation of β-amyloid: positive PET image of an increase in cerebral amyloid load and a reduction in the levels of Aβ 42 in cerebrospinal fluid (CSF).
2. Biomarkers of degeneration or neuronal damage: hypometabolism of FDG in PET; the increase in tau protein and phosphorylated tau in CSF and cerebral atrophy evaluated in MR of the hippocampus, entorhinal cortex, and lateral and/or parietal, medial and basal temporal cortex.

Changes in these biomarkers seem to follow a temporal pattern with a deposit of β-amyloid in the brain at the onset, followed by evident neurodegeneration and finally, the appearance of clinical symptoms. At the time episodic memory becomes impaired, the amyloid load has reached a plateau and remains relatively stable, while the markers of neurodegeneration become positive and worsen and the clinical manifestations progress.

Thus, the new guidelines involve a definition of AD, with an asymptomatic onset of unknown duration, a symptomatic period which does not compromise the autonomy of the patient and a final phase of severe cognitive impairment of dementia. These 3 phases constitute the temporal spectrum of AD which is now known as a “continuum”21,22 (Fig. 3) with 3 stages:

1. Preclinical stage: the earliest, defined by changes in biomarkers but without clinical manifestations in the patient.
2. MCI due to AD: with a nucleus consistent with the clinical criteria which define it.
3. Dementia: clinical impairment with the alterations described by biomarkers.

The AD is no longer identified with the stage of dementia, as it has been up to now, but rather that dementia is the end of the process. Between these 3 phases there is overlapping, and it may be difficult to identify the exact time of transition from one to another. The term MCI due to AD has been proposed to describe this second prodromic or predementia phase; and it is in the MCD phase and in the preclinical manifestations that new therapeutic options should be sought.

PET neuroimaging with 18F-FDG has a central role in this panel of biomarkers, detecting the underlying alterations in metabolism and pathological changes at the beginning of the MCI phase and dementia in vivo. On the other hand, PET neuroimaging of amyloid allows early detection of the presymptomatic phases of AD in addition to constituting a criteria to exclude other different causes of AD in the clinical context of MCI or dementia.23,24 Nonetheless, the generation of knowledge in this field is produced at a great speed, thereby explaining the continuous appearance of new proposals for modifying or completing previous proposals and the need for continuous updating.25–28

This occurs to such an extent that recently the Society of Nuclear Medicine and Molecular Imaging (SNMIM) & Alzheimer Association published some criteria of the appropriate and inappropriate use of cerebral amyloid imaging studies based on the consensus of experts which analyzed numerous clinical scenarios in which this study may be applied.27 In this sense, this has led to a taking of positions on behalf of other authors who have pointed out the restrictive nature of this list of indications, underlining the importance of not assuming them as a clinical guideline but that more aspects, still insufficiently known, should be contemplated such as the correlation of amyloid imaging with other biomarkers, especially 18F-FDG-PET and adequate assessment of the cost-benefits of the study.28

In our opinion, it is still early to know the full potential of the technique in depth. In the future it will be defined by the development of efficacious treatments. Nonetheless, the criteria proposed are useful to guide the indications in a health care context. The incorporation of studies with cerebral amyloid tracers in our specialized health care context is having an important impact on the diagnostic characterization of patients with cognitive impairment, contributing to the differential diagnosis of these processes and providing reliable knowledge to neurologists in their practical approach.

β-Amyloid

β-Amyloid is the principal component of the amyloid plaques characteristic of AD. β-Amyloid may contain 40 or 42 amino acids which fold into fibrils with a lamellar structure and may bind stains such as congo red and the S dand T thioflavins.29 The β-amyloid protein is highly polymorphous and may assume a range of quaternary structures which have different biological and neurotoxic properties. It is formed after sequential excision from the amyloid precursor protein (APP) by the successive action of beta and gamma secretases and forms dimers and oligomers which may progress to insoluble polymers or large disordered aggregates.30

Cerebral deposit of β-amyloid is an early event in the process of the disease which may occur more than one decade before the person demonstrates clinical symptoms of AD.31 PET amyloid tracers provide a quantitative measure of the insoluble cortical amyloid load in vivo, have low affinity by fibrillar amyloid and their binding to the non physiological β-amyloid binding sites is reversible and may be blocked by “cold” thioflavin. Although the target of these tracers is fibrillar β-amyloid, they are not specific for a particular pool of β-amyloid but rather should be considered as a general marker of cerebral amyloid load. The mechanisms of production and clearance of β-amyloid have become the object of investigations of new therapeutic targets, investigating passive antiamyloid immunotherapies, clinical trials with secretase inhibitors and anti-amyloid immunization.32 In this context, quantification of the PET image of amyloid may play an important role.

The image of amyloid by positron emission tomography: 11C-PIB

**Equipment:** positron emission tomography in the study of cerebral function

PET is a molecular imaging technique which provides knowledge as to the distribution of a positron emitting radiotracer in the organism or in a specific organ such as the brain. Thus, when a positron is emitted from the nucleus of an atom it travels only a few millimeters until interacting with an electron, being annihilated in 2 photons of 511 keV which move away, forming a 180° angle.
Tomographers are therefore equipped with scintillation detector rings such as bismuth germanate (BGO) or lutetium orthosilicate (LSO) which register events in coincidence with a temporal window of a few nanoseconds. The positron emitters most frequently used for cerebral imaging are $^{15}$O (t½ approx. 2 min), $^{11}$C (t½ approx. 20 min) and $^{18}$F (t½ approx. 110 min), and the spatial resolution of the current PET tomographs ranges between 3 and 8 mm.

The great strength of PET imaging is the possibility of studying and measuring specific aspects of cerebral function when an adequate radiotracer is available. Thus, there is a lengthy list of PET radiotracers which assess cerebral blood flow, cerebral glucolytic metabolism ($^{18}$F-FDG), cholinergic neurotransmission (nicotinic, muscarinic and acetyl-cholinesterase receptors), dopaminergic, serotoninergic neurotransmission, benzodiazepinic receptors, and others related to neurooncology (DNA synthesis, hypoxia or synthesis of amino acids). Recent investigation on the contribution of a radiotracer such as $^{11}$C-PIB is allowing the obtention of data which was previously only possible in autopsies.

\textbf{β-Amyloid radiotracers: in vitro and in vivo development}

The search for this radiotracer was initiated years ago with extensive basic in vitro and in vivo investigation in animal models. Numerous molecules have been studied, among those derived from congo red such as chrysamine G, thioflavin and its derivatives, stilbene derivatives, acridine orange and DNNP derivatives were of note. An early attempt at obtaining amyloid PET images in vivo in humans was performed by Shoghi-Jadid et al. in 2002 with the use of $^{18}$F-FDNNP in a group of 9 patients with AD and 7 controls. In this study absolute retention of $^{18}$F-FDNNP was observed in the frontal, parietal, temporal and occipital regions which exceeded the reference region (the protuberance) from 10 to 15%, showing greater retention of the radiotracer (30% greater than the region of reference) in the hippocampus, amygdala and entorhinal cortex.

In parallel, in 2003 Mathis et al. developed $^{11}$C-6-OH BTA-1, which began to be known as Pittsburg compound B or PIB, observing its binding to the frontal cortex in autopsy brains. In 2003, Bacska et al. validated the molecule in a transgenic murine model of AD, demonstrating its uptake by amyloid plaque in mice with AD at 3 min after intravenous administration, being rapidly cleared in healthy mice.

In Uppsala, Sweden in 2004 Klunk et al. performed the first study with $^{11}$C-PIB in humans in a group of 16 patients with mild AD (MMSE 18–28) and 9 healthy controls. A robust difference was observed between the level and the pattern of PIB retention in patients with AD compared with the healthy controls. The $^{11}$C-PIB presented a more important retention in the frontal cortex (2-fold greater than in controls) while the retention was similar in relatively preserved areas of amyloid deposit (subcortical white matter, protuberance and cerebellum). An inverse correlation was also found between the grade of cerebral metabolism measured by FDG-PET and the retention of $^{11}$C-PIB in the parietal lobe.

$^{11}$C-PIB: \textit{kinetics as a radiotracer and parameters of acquisition of positron emission tomography imaging}

The objective of investigations to make amyloid imaging studies feasible was to determine the regional distribution and the concentration of β-amyloid plaques in vivo. The characteristics required for a β-amyloid radiotracer would be: (1) high affinity and selectivity by the β-amyloid structure. (2) Low molecular weight and mild lipophilia: passage through the hematocerebral barrier, high initial uptake and rapid clearance. (3) High cerebral stability with metabolites which are not reuptaken. (4) Possibility of being labeled with positron emitters, and (5) clinical availability.

$^{11}$C-PIB ($\text{N-methyl-$^{11}$C}$2-[4-methylamino-phenyl]-6-hydroxybenzotiazole) was the first specific tracer for β-amyloid plaques with high affinity for insoluble compounds and low affinity for the soluble or amorphous compounds and is considered as the reference of amyloid cerebral imaging. It is a derivative of thioflavin T, a stain for histologic staining of dense plaques which can be labeled with $^{11}$C. The PET tracers developed to date have a low affinity for diffuse plaque which is why the PET may be negative when there are only diffuse plaques. The distribution pattern of $^{11}$C-PIB has been adequately correlated with the percentage of amyloid load determined with staining in cerebral autopsy tissues. This radiotracer provided the first images of β-amyloid plaques in vivo, allowing the study of the biodistribution of the radiotracer in the different cerebral regions and has allowed the establishment of patterns of uptake in patients with AD.

The clearance of $^{11}$C-PIB has different patterns according to the cerebral region. Its binding to gray matter is specific and reversible, and the binding to white matter is unspecific and not satureable. Patients with AD have greater cortical retention than controls with the same age range. These studies may be reliably visually interpreted in terms of positive/negative clearance and, if not, they are considered as not diagnostic. Although it has been described that a study is considered positive if the cortical uptake of the radiotracer is greater or equal to the uptake of white matter and that the sole presence of cortical retention of $^{11}$C-PIB indicates cerebral deposit of β-amyloid (Fig. 4), the concrete significance of these considerations for their general application remains the object of evaluation.

The quantification methods used differ if aimed toward a clinical application (static studies) in which the calculation of the region/cerebellum ratio to a determined time post-injection of the radiotracer is reliable or if performed within a context of investigation with dynamic studies. In this framework of investigation using the Logan method we can use multiple time graphic analysis (MTGA) for reversible uptakes and the distribution volume/ratio (DVR) with reference in the cerebellum.

Most studies use the cerebellar gray matter as the region of reference. The amyloid plaque here is usually much less dense; however, in some circumstances it may not be recommended such as in familial AD and in very advanced stages of dementia in which protuberance is recommended. The cortical–cerebellar binding ratio provides a reliable measure of cerebral amyloid load and is expressed as the cortical/cerebellar SUV ratio. It is estimated once an apparent stationary equilibrium has been achieved at 40–50 min after the administration of the radiotracer, with a time of study acquisition of between 20 and 30 min. Only the cortical regions are considered, where it is known that the amyloid plaques accumulate. The SUV ratio varies between 1.3 and 1.6 as the upper threshold of normality, depending on the size and localization of the cortical and cerebellar ROI.
The significance of the uptake of 

This observation is reported in 33/106 healthy volunteers. These data show a similar topographic pattern in the posterior cingulate gyrus, anterior cingulate and frontal cortex. Within this group, MCD with amnestic predominance more frequently presents retention of $^{11}$C-PIB than the non amnestic patients without cognitive alteration is not always associated with the cerebral anatomopathological distribution of dense $^{11}$C-amyloid plaques. Regional binding is greater in the frontal cortex, cingulate gyrus, precuneus, and the striate, parietal and lateral temporal cortices. To the contrary, there is lesser binding in the occipital cortex, sensory and motor cortex and in the mesial temporal cortex ($^{11}$C-amyloid load, $^{11}$C-PIB, correlation with the FDG-PET image, magnetic resonance and other biomarkers).

In autopsy series it has been demonstrated that the presence of $\beta$-amyloid plaques increases with age and that in studies with volunteers as controls most do not show cortical cerebral retention and, if present, they follow a topographic pattern similar to AD but with less intensity. The significance of the uptake of $^{11}$C-PIB continues under investigation. Lack of uptake has an elevated negative predictive value, but the retention of $^{11}$C-PIB in controls or elderly patients without cognitive alteration is not always associated with the development of AD or MCI.

In patients with MCI cortical cerebral retention of $^{11}$C-PIB is observed in up to two thirds of the patients, with intermediate uptake/retention between those with AD and the controls and with a similar topographic pattern in the posterior cingulate gyrus, anterior cingulate and frontal cortex. Within this group, MCD with amnestic predominance more frequently presents retention of $^{11}$C-PIB than the non amnestic patients.

The behavior of $^{18}$F-FDG in the brain of these patients has also been studied and contrasted with the retention of $^{11}$C-PIB, showing an inverse correlation; that is, hypometabolism of $^{18}$F-FDG is usually associated in those regions with greater retention of $^{11}$C-PIB, being more intense with greater retention, except in the hippocampus where the hypometabolism is more severe in AD than in MCI, but there is no retention of $^{11}$C-PIB. This observation is probably related to the asynchronic development of neurofibrillar tangles of tau protein and amyloid plaques which are discordant in this region for unknown causes in the “continuum” of AD.

According to recent studies, the increase in $\beta$-amyloid load, measured by the retention of $^{11}$C-PIB, has shown to be different in each stage of the disease. Thus, in controls or healthy volunteers, this load remains practically unvaried at 2–3 years of follow up while significantly varying in most patients with MCI and with a much lower increase in time if the patient is already in the phase of dementia. Simultaneously, the consumption of glucose diminishes over time in normal controls. This descent accelerates in patients with MCI and shows a more severe temporal decrease – hypometabolism – which accelerates within a short time in the phase of dementia. Therefore, the uptake of $^{11}$C-PIB increases with age in controls while the FDG diminishes.

Structural impairment is not associated with significant increases in $^{11}$C-PIB and thus, when MR reveals structural changes these have been produced much earlier than the alterations in, first, the studies with $^{11}$C-PIB and after in those with $^{18}$F-FDG. No strong correlation has been observed between the uptake of $^{11}$C-PIB and the grade of cognitive impairment, and it is known that the presence of neurofibrillar tangles has a greater correlation with the degree of cognitive impairment of AD than the quantity of $\beta$-amyloid plaques. The cortical retention of $^{11}$C-PIB presents an inverse association with the presence of $\beta$-amyloid in CSF and shows a direct correlation with the tau protein in CSF.

**Elderly patients without cognitive impairment**

Several studies have demonstrated that the retention of $^{11}$C-PIB is increased in many cognitively normal older persons, and that the prevalence of cerebral amyloid deposits depends on the age and the threshold chosen to define it as a positive PIB study. These data are in agreement with post-mortem histologic studies which have detected significant amyloid loads in 25–45% of the people over 75 years of age. Villemagne et al. reported 33/106 healthy volunteers with a positive PIB study (31%), with predominant retention of PIB in the prefrontal cortical region and the posterior cingulate. At 3

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**Fig. 5.** Studies with $^{18}$F-FDG and $^{11}$C-PIB in a normal subject (upper row), a subject with MCI (middle row) and a subject with dementia due to AD (bottom row).

**Fig. 6.** (A) PET study with negative $^{11}$C-PIB in a patient with non amnestic MCI. (B) PET study with positive $^{11}$C-PIB in a patient with amnestic MCI.
years, 8 of these 33 controls with a positive PIB developed MCI or AD, and, on the other hand, only one of the healthy PIB negative volunteers did so.

In general, the deposit of PIB is increased in one third of cognitively normal elderly subjects in what seems to be an age dependent process which begins more than one decade before the appearance of cognitive symptoms. The clinical implications of these findings are under investigation. In a patient with a PIB negative study, progression to MCI or AD is very improbable.53

On the other hand, the positive predictive value of a PIB study is less clear, since, on occasions, there may be subtle clinical alterations which have remained unnoticed or in which other concomitant processes may intervene.54 Longitudinal term studies are still necessary to determine whether an elevated deposit of cerebral amyloid predicts a future evolution toward AD or confirms the model of the amyloid cascade with a long presymptomatic phase of the disease.

**Prognostic value of the 11C-PIB image in the context of mild cognitive impairment**

This is a crucial question in the application of these results to the reality of health care which also requires results in longitudinal studies. In general terms, the data available indicate that approximately two thirds of the patients with MCI of amnestic predominance and PIB positive progress toward the phase of AD in around 3 years and very few progress in this direction (7%) if their study was PIB negative.44,54 Other longitudinal studies reinforce the observation that the probability of progression of patients with MCI toward the phase of dementia is much greater if they are PIB positive than PIB negative.

Different factors seem to influence in this progression: the age of the patients included in these study groups, the percentage of APOEe carriers, the grade of basal impairment and factors of protection such as the years of education, but, in general, a cortical increase of PIB retention (PIB positive) in patients with MCI is quite predictive of future conversion to AD, while PIB negative patients with MCI progress much less to dementia, and if they do so, they usually develop a non Alzheimer dementia.45,52,53,55

**Limitations of imaging with 11C-PIB**

The physiopathology of AD remains unknown, and although the theory of the amyloid cascade constitutes a model with strong evidence, some aspects are not well explained. Thus, the significance of the important retention in the frontal lobes still does not have a solid explanation, and the variants observed in the distribution pattern require investigation within a wider framework.48,56 On the other hand, it has been indicated that the size of the amyloid plaques may condition the performance of the technique as may the nature of these aggregates (if the plaque is dense or diffuse), since only dense plaque is manifested with this radiotracer.40 Other questions, such as the limitations by partial volume or the interference of the signal from the periventricular white matter are inherent to the study and do not significantly influence interpretation. It is also convenient to know that cerebral amyloid deposits may be found in amyloid angiopathy and in some cases of Lewy body disease.

**Amyloid images with fluorinated tracers**

PET imaging with 11C-PIB requires the availability of a cyclotron and a radiochemistry laboratory for its production in situ. The labeling of β-amyloid tracers with fluorine has the advantage of the availability of this technology for clinical use and investigation in contexts in which a cyclotron is not available. They correlate well with studies with 11C-PIB in the context of AD, even when they have lesser cerebral extraction, and in the interpretation of the image it is necessary to take into account the greater contribution of the unspecific signal proceeding from the cerebral white matter. It seems that the β-amyloid tracers with 18F have a similar diagnostic and prognostic performance, but longitudinal studies are lacking. Uptake has also been reported in populations considered as healthy controls.57 18F-FDDNP was the first tracer to be labeled with 18F, but it predominantly binds to the neurofibrillar tangles and only 10% of the uptake specifically proceeds from their binding to amyloid plaques.33 Thus, differential diagnosis in MCI is not useful because it does not present a bimodal distribution which differentiates between that linked to AD and that which is not. One of its characteristics is that it competes with the binding sites of the NSAIDS in the amyloid plaque.58 11C-PIB and 18F-FDDNP do not have the same targets, with 11C-PIB being more appropriate for characterizing the etiology of MCI.18F-flutemadil is a thioflavin labeled with 18F which only differs from 11C-PIB in one molecule of 18F in position 3. This tracer with 18F has the greatest affinity for β-amyloid with similar patterns to those of 11C-PIB but the retention in white matter and protuberance is greater than with 11C-PIB. The binding to the amyloid achieves a plateau at 90 min while the clearance of the unspecific binding is seen at around 30 min. These kinetics are more inadequate than those of other fluorinated tracers such as florbetaben or florbetapir but, among these 3 compounds, it has the greatest affinity for the amyloid. Florbetapir has recently been approved by the FDA for clinical use and florbetaben is in a phase III clinical trial (Table 3).50–51

**Future lines: image of neurofibrillar tangles and amyloid**

In contrast with the deposit of amyloid plaques, neuropathological studies indicate that the density of the neurofibrillar tangles is correlated with degeneration and cognitive impairment. An increased presence is not observed in cognitively normal individuals. The determination of tau protein and phospho-tau in CSF is a reliable biomarker of neurodegeneration, but lumbar puncture does not provide information on the regional cerebral distribution of the same. Thus, it does not provide this important information for therapeutic management or response to treatment. If investigation continues, molecular imaging with tau-specific radiotracers could provide precise, reliable and reproducible information in quantitative terms of the total and regional load of tau which is useful to study the physiopathology of Alzheimer and tauopathies in depth. On the other hand, it would contribute to evaluation of the progression and severity of AD and the design of clinical trials with adequate selection of patients with the aim of developing therapies in neurodegenerative dementias of the Alzheimer and non Alzheimer types in which tau plays a central role.62

We therefore have 2 fundamental aspects for the knowledge of and investigative development in the cognitive impairment linked to Alzheimer and non Alzheimer diseases: molecular imaging of β-amyloid for early and differential diagnosis of the preclinical phases of MCI and AD and the tau protein as a marker of damage and specific progression in tauopathies. In this way we can know and monitor the development of the evaluative stages described by Braack in AD. On the other hand, the role of neuroinflammation is currently under study and may improve the comprehension of the physiopathology of the disease.63

In conclusion, the availability of specific tracers, directed at the preclinical and clinical phases of AD such as the amyloid-specific tracers and perhaps the tau-specific tracers is converting molecular neuroimaging into a safe diagnostic pillar of the knowledge of these syndromes and will allow reasonably guided advances toward the development of effective therapies for these patients which, in this day and age, are a great challenge in this field.
Table 3
Fluorinated amyloid radiotracer.

<table>
<thead>
<tr>
<th>Radiotracer</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>11C-PiB</td>
<td>• Radiotracer of reference with neuropathologic validation.</td>
</tr>
<tr>
<td>11F-Flutemetamol</td>
<td>• Affinity for binding $K_A$: $0.87 \pm 0.18 \text{nmole/L}$</td>
</tr>
<tr>
<td>18F-Florbetaben</td>
<td>• Very slow clearance kinetics/Imagery obtained at 90'.</td>
</tr>
<tr>
<td>18F-Florbetapir</td>
<td>• Uptake pattern similar to $^{11}$C-PiB with greater retention in white matter</td>
</tr>
<tr>
<td>18F-AV-1</td>
<td>• Affinity for binding $K_A$ similar to $^{11}$C-PiB ($0.74 \pm 0.38 \text{nmole/L}$)</td>
</tr>
<tr>
<td>18F-AV-45</td>
<td>• Cortical SUVR: AD: 2.37/healthy controls: 1.4</td>
</tr>
<tr>
<td>11C-PIB PET</td>
<td>• Slow clearance kinetics/images obtained at 90'.</td>
</tr>
<tr>
<td>11F-PIB PET</td>
<td>• Uptake pattern similar to $^{11}$C-PiB but with lesser intensity of uptake.</td>
</tr>
<tr>
<td>11C-PIB PET</td>
<td>• Affinity for binding $K_A &lt; $ to $^{11}$C-PiB ($K = 2.87 \pm 0.17 \text{nmole/L}$)</td>
</tr>
<tr>
<td>11C-PIB PET</td>
<td>• Cortical SUVR: AD: 2.02–1.93/healthy controls: 1.29–1.29</td>
</tr>
</tbody>
</table>

Source: Refs. 59–61.

Points of interest

1. Alzheimer’s disease has currently been redefined as an alteration of the “cognitive continuum” with 3 temporal phases: a) Presymptomatic phase. b) Phase of mild cognitive impairment. c) Phase of dementia.
2. Each phase of the disease is characterized by a nucleus of clinical criteria (mild cognitive impairment and dementia) and qualified in its probability that this cognitive impairment is due to Alzheimer’s disease because of a group of biomarkers, classified as an accumulation of amyloid and damage.
3. Amyloid imaging with $^{11}$C-PiB PET is a method to evaluate the cerebral deposit of amyloid and has a value similar to the determination of Aβ-42 amyloid in CSF. It is a biomarker of accumulation of β-amyloid in the cerebral cortex (and, if positive, indicates a high probability that the cognitive impairment of a patient is due to AD).
4. $^{11}$C-PiB is a radiotracer of reference to assess the deposit of fibrillar β-amyloid in the cerebral cortex through its retention.
5. The characteristic distribution pattern in a positive study is the retention of $^{11}$C-PiB predominantly in the frontal, parietal, lateral temporal and precuneus/posterior cingulate regions.
6. It is not used to evaluate the intensity or severity of dementia.
7. The use of fluorinated radiotracers for the detection of β-amyloid may be useful when a cyclotron is not available for the synthesis of $^{11}$C-PiB.

Conflict of interests

The authors declare no conflict of interests.

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