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# A $\beta$ Imaging in Aging, Alzheimer's Disease and Other Neurodegenerative Conditions

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## Abstract

In vivo imaging of  $\beta$ -amyloid (A $\beta$ ) has transformed the assessment of A $\beta$  pathology and its changes over time, extending our insight into A $\beta$  deposition by providing highly accurate, reliable and reproducible quantitative statements of regional or global A $\beta$  burden in the brain, essential for therapeutic trial recruitment and for the evaluation of anti-A $\beta$  treatments. Although cross-sectional evaluation of A $\beta$  burden does not strongly correlate with cognitive impairment in AD, it does correlate with memory impairment and a higher risk for cognitive decline in the aging population and MCI subjects. This correlation with memory impairment, one of the earliest symptoms of AD, suggests that A $\beta$  deposition is not part of normal aging, supporting the hypothesis that A $\beta$  deposition occurs well before the onset of symptoms. Longitudinal observations, coupled with different disease-specific biomarkers to assess potential downstream effects of A $\beta$ , are required to confirm this hypothesis and further elucidate the role of A $\beta$  deposition in the course of Alzheimer's disease.

## 10.1 Introduction

Alzheimer's disease (AD) is a progressive and irreversible neurodegenerative disorder clinically characterised by memory loss and cognitive decline that severely affect the activities of daily living (Masters et al. 2006). AD is the principal cause of dementia in the elderly, leading invariably to death, usually within 7–10 years after diagnosis (Khachaturian 1985). The progressive nature of the neurodegeneration suggests an age-dependent process that ultimately leads to synaptic failure and neuronal damage in cortical areas of the brain essential for memory and other cognitive domains (Isacson et al. 2002). AD not only has devastating effects on the sufferers and their caregivers, but it also has a tremendous socioeconomic impact on families and the health system, a burden which will only increase in the upcoming years as the population of most countries ages (Johnson et al. 2000). In the absence of reliable biomarkers, direct pathological examination of brain tissue derived from either biopsy or autopsy remains the only definitive method for establishing a diagnosis of AD (O'Brien et al. 2000). The typical macroscopic picture is gross cortical atrophy, while microscopically, there is widespread cellular degeneration and diffuse

synaptic and neuronal loss, accompanied by reactive gliosis and the presence of the pathological hallmarks of the disease: intracellular neurofibrillary tangles (NFT) and extracellular amyloid plaques (Jellinger 1990; Masters 2005; Masters and Beyreuther 2005). While NFT are intraneuronal bundles of paired helical filaments mainly composed of the aggregates of an abnormally phosphorylated form of tau protein (Jellinger and Bancher 1998; Michaelis et al. 2002), neuritic plaques consist of dense extracellular aggregates of  $\beta$ -amyloid (A $\beta$ ) (Masters et al. 1985), surrounded by reactive gliosis and dystrophic neurites. A $\beta$  is a 4 kDa 39–43 amino acid metalloprotein derived from the proteolytic cleavage of the amyloid precursor protein (APP), by  $\beta$ - and  $\gamma$ -secretases (Cappai and White 1999). To date, all available genetic, pathological, biochemical and cellular evidence strongly supports the notion that an imbalance between the production and removal of A $\beta$  leading to its progressive accumulation is central to the pathogenesis of AD (Villemagne et al. 2006). The 'A $\beta$ centric theory' (Masters et al. 2006) postulates that A $\beta$  plaque deposition is the primary event in a cascade of effects that lead to neurofibrillary degeneration and dementia (Hardy 1997).

Despite the proposed new diagnostic criteria (McKhann et al. 2011), the clinical diagnosis of AD is still largely based on progressive impairment of memory and decline in at least one other cognitive domain and by excluding other diseases that might also present with dementia such as frontotemporal lobar degeneration (FTLD), dementia with Lewy bodies (DLB), stroke, brain tumour, normal pressure hydrocephalus or depression (Larson et al. 1996; Cummings et al. 1998). A variable period of up to 15 years of prodromal decline in cognition characterised by a relatively isolated impairment in short-term memory that may also be accompanied by impairments of working memory, known as amnesic mild cognitive impairment (MCI), usually precedes the formal diagnosis of AD (Petersen et al. 1999; Petersen 2000). At this point, there is no cure for AD nor proven way to slow the rate of neurodegeneration. Symptomatic treatment with an acetylcholinesterase inhibitor or a glutamatergic moderator provides modest benefit in some patients usually by temporary stabilisation rather than a noticeable improvement in memory function (Masters and Beyreuther 2006).

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## 10.2 A $\beta$ Imaging Radiotracers

A $\beta$  plaques and NFT are the hallmark brain lesions of AD. These microscopic aggregates are still well beyond the resolution of conventional neuroimaging techniques used for the clinical evaluation of patients with AD. Positron emission tomography (PET) is a sensitive molecular imaging technique that allows in vivo quantification of radiotracer concentrations in the picomolar range, allowing the noninvasive assessment of molecular processes at their sites of action, detecting disease processes at asymptomatic stages when there is no evidence of anatomic changes on computed tomography (CT) and magnetic resonance imaging (MRI) (Phelps 2000). Since A $\beta$  is at the centre of AD pathogenesis and given that several pharmacological agents aimed at reducing A $\beta$  levels in the brain are being developed and tested, many efforts have been focused on generating radiotracers for

**Table 10.1** Potential applications of A $\beta$  imaging

Accurate diagnosis of A $\beta$ pathology
Prognosis of conversion to AD
Assessment of the spatial and temporal pattern of A $\beta$ deposition and its relation to disease progression, cognitive decline and other disease biomarkers
Early detection of Alzheimer's disease pathology, allowing disease-specific interventions when cognition is unimpaired or minimally impaired
Subject selection for anti-A $\beta$ trials
Predict response to anti-A $\beta$ therapy
Monitor the effectiveness of anti-A $\beta$ therapy

imaging A $\beta$  in vivo (Sair et al. 2004; Mathis et al. 2005; Villemagne et al. 2005). Several applications of A $\beta$  imaging have been proposed (Table 10.1).

As a quantitative neuroimaging probe, the A $\beta$  radiotracer must possess a number of key general properties: it should be a lipophilic, nontoxic small molecule with a high specificity and selectivity for A $\beta$ , amenable for high specific activity labelling with  $^{18}\text{F}$  or other long lived radioisotope, with no radiolabelled metabolites that enter the brain, while reversibly binding to A $\beta$  in a specific and selective fashion (Laruelle et al. 2003; Nordberg 2004; Pike 2009). Overall, binding affinity and lipophilicity are the most crucial properties for in vivo neuroimaging tracers. While high affinity for A $\beta$  is desirable to provide an adequate signal-to-noise ratio, this high affinity might also delay reaching binding equilibrium requiring an extended scanning time. And while lipophilicity is necessary for the tracer to cross the blood-brain barrier (BBB), if the radiotracer is too lipophilic, its nonspecific binding might be too high (Laruelle et al. 2003; Pike 2009).

Through the years, several compounds have been evaluated with different fortune as potential A $\beta$  probes: monoclonal and anti-A $\beta$  antibodies fragments, serum amyloid P, basic fibroblast growth factor, A $\beta$  fragments, derivatives of histopathological dyes such as Congo red, chrysamine G and thioflavin S and T (*for review, see* (Villemagne and Rowe 2010)). While selective tau imaging for in vivo NFT quantification is still in the early stages of development (Okamura et al. 2005; Maruyama et al. 2009; Ojida et al. 2009; Fodero-Tavoletti et al. 2011), several A $\beta$  radiotracers found their way into human clinical trials.

Almost a decade after unsuccessful trials with anti-A $\beta$  antibodies (Majocha et al. 1992), A $\beta$  imaging came to fruition with the first report of successful imaging in an AD patient with  $^{18}\text{F}$ -FDDNP, a tracer claimed to bind both plaques and NFT (Shoghi-Jadid et al. 2002). Since then, human A $\beta$  imaging studies have been conducted in AD patients, normal controls and patients with other dementias using  $^{11}\text{C}$ -PiB (Klunk et al. 2004),  $^{11}\text{C}$ -SB13 (Verhoeff et al. 2004),  $^{11}\text{C}$ -ST1859 (Bauer et al. 2006),  $^{11}\text{C}$ -BF-227 (Kudo et al. 2007),  $^{11}\text{C}$ -AZD2138 (Nyberg et al. 2009),  $^{18}\text{F}$ -florbetaben (Rowe et al. 2008),  $^{18}\text{F}$ -flutemetamol (Serdons et al. 2009a),  $^{18}\text{F}$ -florbetapir (Wong et al. 2010) and  $^{18}\text{F}$ -AZD4694 (Cselenyi et al. 2012) with PET.

In order to test compounds that could have more widespread application, preliminary studies with SPECT A $\beta$  radiotracers  $^{123}\text{I}$ -CQ (Opazo et al. 2006) and  $^{123}\text{I}$ -IMPY (Newberg et al. 2006) showed limited utility for the evaluation of A $\beta$

burden in AD, although  $^{123}\text{I}$ -IMPY might be useful in the evaluation of transmissible spongiform encephalopathies (Song et al. 2008). New SPECT radiotracers labelled with  $^{123}\text{I}$  or those that could be potentially labelled with  $^{99\text{m}}\text{Tc}$  are being evaluated (Qu et al. 2007a, b; Serdons et al. 2007; Lin et al. 2009).

While all of the aforementioned tracers bind with varying degrees of success to A $\beta$  fibrils and brain homogenates of AD patients, Congo red and thioflavin T—and some of their derivatives—have recently been shown to also bind to soluble oligomeric forms of A $\beta$  (Maezawa et al. 2008). On the other hand, A $\beta$  soluble species represent less than 1 % of the total brain A $\beta$  (McLean et al. 1999), and the reported affinity of PiB for these soluble oligomers seems to be significantly lower than for A $\beta$  fibrils (Maezawa et al. 2008). Until highly selective radiotracers are developed to bind the A $\beta$  soluble species, the contribution of these oligomers to the PET signal in sporadic AD from tracers such as  $^{11}\text{C}$ -PiB is considered to be negligible (Mathis et al. 2007).

### 10.2.1 $^{11}\text{C}$ -Labelled Radiotracers

#### $^{11}\text{C}$ -PiB

$^{11}\text{C}$ -PiB (PiB), the most successful and widely used of the currently available A $\beta$  tracers, has been shown to possess high affinity and high selectivity for fibrillar A $\beta$  in plaques and other A $\beta$ -containing lesions (Klunk et al. 2001; Mathis et al. 2002, 2005; Price et al. 2005; Ye et al. 2005; Cohen et al. 2012). In vitro studies with high specific activity  $^3\text{H}$ -PiB demonstrated two binding sites for PiB in brain homogenates and A $\beta_{1-42}$  fibrils (Klunk et al. 2005). Recent studies have shown that  $^{11}\text{C}$ -PiB binds with high affinity to the N-terminally truncated and modified A $\beta$  and A $\beta\text{N3}$ -pyroglutamate species in senile plaques (Maeda et al. 2007). In vitro assessment of  $^3\text{H}$ -PiB binding to white matter homogenates failed to show any specific binding (Fodero-Tavoletti et al. 2009b). PiB is a derivative of thioflavin T, a fluorescent dye commonly used to assess fibrillisation into  $\beta$ -sheet conformation (LeVine 1999), and as such PiB has been shown to bind to a range of additional A $\beta$ -containing lesions including diffuse plaques and cerebral amyloid angiopathy (CAA) (Lockhart et al. 2007), as well as to A $\beta$  oligomers—although with lower affinity (Maezawa et al. 2008). PiB also displayed lower affinity towards other misfolded proteins with a similar  $\beta$ -sheet secondary structure such as  $\alpha$ -synuclein (Fodero-Tavoletti et al. 2007; Ye et al. 2008) and tau (Lockhart et al. 2007; Ikonovic et al. 2008). This is relevant particularly since AD has been described as a ‘triple brain amyloidosis’ (Trojanowski 2002). Most importantly, these studies have shown that, at the concentrations achieved during a PET scan,  $^{11}\text{C}$ -PiB cortical retention in AD or DLB primarily reflects A $\beta$ -related cerebral amyloidosis and not binding to Lewy bodies (LB) or NFT (Klunk et al. 2003; Fodero-Tavoletti et al. 2007; Lockhart et al. 2007; Ikonovic et al. 2008).  $^{11}\text{C}$ -PiB has consistently provided quantitative information on A $\beta$  burden in vivo, contributing new insights into A $\beta$  deposition in the brain, allowing earlier detection of AD pathology (Klunk et al. 2004; Mintun et al. 2006; Rowe et al. 2007; Cohen et al. 2012) and accurate differential diagnosis of the dementias (Ng et al. 2007b; Rabinovici et al. 2007; Rowe et al. 2007).

### **<sup>11</sup>C-BF-227**

<sup>11</sup>C-BF-227 (BF-227), a benzoxazole derivative, is also a promising tool as an A $\beta$  imaging tracer (Okamura et al. 2004). In vitro binding studies with BF-227 demonstrated a K<sub>i</sub> value of 4.3 nM for the compound to A $\beta$ <sub>1-42</sub> fibrils (Kudo 2006). A PET study using BF-227 showed AD patients were clearly distinguishable from age-matched controls with AD patients displaying significantly higher tracer retention in the cerebral cortex than controls (Kudo et al. 2007). Regional parametric analysis of the images further demonstrated a higher BF-227 retention in the posterior association cortex in AD patients. Unlike PiB, BF-227 presents with similar binding affinities for A $\beta$  and  $\alpha$ -synuclein (Fodero-Tavoletti et al. 2009a).

A few other C-11 A $\beta$  radiotracers have been tested in humans. The evaluation of the stilbene derivative, <sup>11</sup>C-SB13, showed that it could differentiate between five AD and six controls but had a lower effect size values when compared with <sup>11</sup>C-PiB (Verhoeff et al. 2004). A preliminary study with the anti-A $\beta$  agent <sup>11</sup>C-ST1859 revealed small differences in radiotracer retention between nine AD patients and three healthy controls, but showing that the biodistribution and specificity of therapeutic agents can be assessed with PET (Bauer et al. 2006). Another A $\beta$  radiotracer, <sup>11</sup>C-AZD2138, showed not only reversible binding but also displayed very low non-specific binding to white matter (Johnson et al. 2009; Nyberg et al. 2009).

## **10.2.2 <sup>18</sup>F-Labelled Radiotracers**

Unfortunately, the 20-min radioactive decay half-life of carbon-11 (<sup>11</sup>C) limits the use of <sup>11</sup>C-PiB to centres with an on-site cyclotron and <sup>11</sup>C radiochemistry expertise, making the cost of studies prohibitive for routine clinical use. To overcome these limitations, several A $\beta$  tracers labelled with fluorine-18 (<sup>18</sup>F; half-life of 110 min) that permits centralised production and regional distribution have been developed and tested. Recent studies with the newly introduced <sup>18</sup>F-labelled A $\beta$ -specific radiotracers, <sup>18</sup>F-florbetapir (Wong et al. 2010; Clark et al. 2011), <sup>18</sup>F-florbetaben (Rowe et al. 2008; Barthel et al. 2011; Villemagne et al. 2011a), <sup>18</sup>F-flutemetamol (Nelissen et al. 2009; Vandenberghe et al. 2010b) and <sup>18</sup>F-AZD4694 (Cselenyi et al. 2012), have been successfully replicating the results obtained with <sup>11</sup>C-PiB. The latest entry into the list of fluorinated A $\beta$  radiotracers is <sup>18</sup>F-MK-3328, developed by Merck, that has the disadvantage that >17 % of its cortical signal was attributed to binding to monoamine oxidase-B (MAO-B) (Sur et al. 2010).

### **<sup>18</sup>F-FDDNP**

A marked progression in the development of A $\beta$  imaging tracers was the synthesis and characterisation by Barrio and colleagues of a very lipophilic radiofluorinated 6-dialkylamino-2-naphthyethylidene derivative that presents nanomolar affinity to A $\beta$  fibrils (Barrio et al. 1999; Agdeppa et al. 2001a, b). <sup>18</sup>F-FDDNP is reported to bind both the extracellular A $\beta$  plaques and the intracellular NFT in AD (Shoghi-Jadid et al. 2002) while also binding to prion plaques in Creutzfeldt-Jakob disease (CJD) brain tissue (Bresjanac et al. 2003). However, in vitro evaluation of FDDNP in concentrations

similar to those achieved during a PET scan showed limited binding to both NFT and A $\beta$  plaques (Thompson et al. 2009).  $^{18}\text{F}$ -FDDNP was used to obtain the first human PET images of A $\beta$  in an 82-year-old woman with AD. AD patients present with higher accumulation and slower clearance of  $^{18}\text{F}$ -FDDNP than controls in brain areas such as the hippocampus (Shoghi-Jadid et al. 2002). Retention time of  $^{18}\text{F}$ -FDDNP in these brain regions was correlated with lower memory performance scores, regional glucose hypometabolism and brain atrophy (Small et al. 2002, 2006). However, the dynamic range of  $^{18}\text{F}$ -FDDNP cortical uptake values between HC and AD patients is small (9 %). Direct comparison of  $^{18}\text{F}$ -FDDNP with  $^{11}\text{C}$ -PiB in monkeys (Noda et al. 2008) and in human subjects showed very limited dynamic range of  $^{18}\text{F}$ -FDDNP (Shih et al. 1987; Tolboom et al. 2009b) and, in a longitudinal study, was found to be less useful than  $^{11}\text{C}$ -PiB and  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) for examining disease progression (Ossenkoppele et al. 2012). Interestingly,  $^{18}\text{F}$ -FDDNP still remains the only A $\beta$  tracer showing retention in the medial temporal cortex of AD patients (Shih et al. 1987) and correlation with cerebrospinal fluid (CSF) tau (Tolboom et al. 2009b).

### **$^{18}\text{F}$ -AZD4694**

Developed by AstraZeneca, the most salient features of  $^{18}\text{F}$ -AZD4694 are, as with  $^{11}\text{C}$ -AZD2138, fast tracer kinetics and low nonspecific binding to white matter, similar to that one observed with  $^{11}\text{C}$ -PiB, suggesting it might be helpful for the detection of small A $\beta$  cortical deposits at very early stages of the disease process (Sundgren-Andersson et al. 2009; Jureus et al. 2010). Initial clinical studies with  $^{18}\text{F}$ -AZD4694 showed a clear distinction in tracer retention between six healthy controls and ten AD patients (Cselenyi et al. 2012).

### **$^{18}\text{F}$ -Florbetaben**

$^{18}\text{F}$ -Florbetaben (a.k.a. AV1; BAY94-9172), synthesised by Kung and colleagues (2005b) and developed by Bayer Healthcare, has been shown to bind with high affinity to A $\beta$  in brain homogenates and selectively labelled A $\beta$  plaques and CAA in AD tissue sections (Zhang et al. 2005b). After injection into Tg2576 transgenic mice, *ex vivo* brain sections showed localisation of  $^{18}\text{F}$ -florbetaben in regions with A $\beta$  plaques as confirmed by thioflavin binding (Zhang et al. 2005a). At tracer concentrations achieved during human PET studies, florbetaben did not show binding to LB or NFT tau in postmortem cortices from DLB or FTLD patients (Fodero-Tavoletti et al. 2012). In human studies, cortical retention of  $^{18}\text{F}$ -florbetaben was higher at 90-min postinjection in all AD subjects compared to age-matched controls and FTLD patients, with binding matching the reported postmortem distribution of A $\beta$  plaques (Rowe et al. 2008). Recently completed phase II clinical studies further confirmed these results (Barthel et al. 2011), and an ongoing longitudinal study in MCI subjects is helping to establish the usefulness of FBB PET in predicting progression to AD (Ong et al. 2010).  $^{18}\text{F}$ -Florbetaben is highly correlated with  $^{11}\text{C}$ -PiB ( $r=0.97$  with a slope of 0.71) (Villemagne et al. 2012c) and was used to detect the presence or absence of AD pathology in the brain in subjects from a wide spectrum of neurodegenerative diseases (Villemagne et al. 2011a). Phase III studies for  $^{18}\text{F}$ -florbetaben have reached completion (Sabbagh et al. 2012).

### **<sup>18</sup>F-Florbetapir**

As <sup>18</sup>F-florbetaben, <sup>18</sup>F-florbetapir is a stilbene derivative that was also synthesised by Kung and colleagues at the University of Pennsylvania (Zhang et al. 2005a) and has been developed by Avid Radiopharmaceuticals. Initial in vitro evaluation showed binding to A $\beta$  plaques in AD brain sections (Choi et al. 2009; Lin et al. 2009). The most salient feature of this tracer is its rapid reversible binding characteristics allowing scanning only at 45–50 min after injection, similar to <sup>11</sup>C-PiB (Wong et al. 2010). <sup>18</sup>F-Florbetapir (Lister-James et al. 2011) has become the most widely used A $\beta$  radiotracer after <sup>11</sup>C-PiB and has been adopted as the A $\beta$  radiotracer for ADNI 2 and also used in patient selection and to evaluate treatment response in a large number of multicenter therapeutic trials around the world. Several multicenter phase I and II studies in AD, MCI and HC showed the ability of <sup>18</sup>F-florbetapir to discriminate between AD and age-matched controls, with ~50 % of the MCI subjects presenting with high <sup>18</sup>F-florbetapir retention (Fleisher et al. 2011). Multicenter studies using <sup>18</sup>F-florbetapir to assess the relationship between A $\beta$  burden and cognition showed that in clinically normal older individuals, A $\beta$  burden in the brain is associated with poorer memory performance (Sperling et al. 2013), while MCI subjects with high A $\beta$  burden in the brain are at a significantly higher risk of cognitive decline over 18 months (Doraiswamy et al. 2012). An initial phase III study in 35 volunteers demonstrated a 96 % agreement between <sup>18</sup>F-florbetapir and neuropathology for the detection of brain A $\beta$  in vivo and no retention in young controls (Clark et al. 2011). An extension phase III in 59 volunteers establishes that <sup>18</sup>F-florbetapir has a sensitivity of 92 % and a specificity of 100 % for the detection of A $\beta$  pathology (Clark et al. 2012). Using a semiquantitative approach, it has been shown that <sup>18</sup>F-florbetapir is >90 % sensitive and specific to detect A $\beta$  pathology in the brain (Camus et al. 2012) and that it is correlated with <sup>11</sup>C-PiB ( $r=0.77$  with a slope of 0.33) (Wolk et al. 2012b). <sup>18</sup>F-Florbetapir (as Amyvid®) is the first radiotracer approved by the Food and Drug Administration (FDA) for detection of A $\beta$  in vivo and the first <sup>18</sup>F-labelled radiotracer approved by the FDA since FDG.

### **<sup>18</sup>F-Flutemetamol**

Another fluorinated tracer, developed by GE Healthcare, that also recently completed a phase III study (Buckley et al. 2012) is <sup>18</sup>F-flutemetamol (a.k.a. GE067) (Serdons et al. 2009a, b). Phase I and II studies demonstrated that <sup>18</sup>F-flutemetamol can differentiate between AD and HC (Nelissen et al. 2009; Vandenberghe et al. 2010b) and that when combined with brain atrophy it could be predictive of disease progression in MCI subjects (Thurfjell et al. 2012). <sup>18</sup>F-Flutemetamol brain retention is also highly correlated with <sup>11</sup>C-PIB ( $r=0.91$  with a slope of 0.90) (Vandenberghe et al. 2010b). Furthermore, there was a high correlation between A $\beta$  burden as measured by <sup>18</sup>F-flutemetamol and by immunohistochemical assessment of brain biopsy tissue (Wolk et al. 2011; Wong et al. 2013).

While the cortical retention of <sup>18</sup>F-florbetapir, <sup>18</sup>F-florbetaben and <sup>18</sup>F-flutemetamol provides a clear separation of AD patients from HC subjects, the degree of cortical retention with <sup>18</sup>F-florbetapir and <sup>18</sup>F-florbetaben is lower than with <sup>11</sup>C-PiB (Villemagne et al. 2012c; Wolk et al. 2012b), showing a narrower dynamic range of



SUVR values, that visually appears as a relatively higher degree of nonspecific binding to white matter. While the cortical retention of  $^{18}\text{F}$ -flutemetamol is similar to that of  $^{11}\text{C}$ -PiB, the nonspecific retention in white matter is much higher (Vandenberghe et al. 2010b). Due to this lower signal-to-noise ratio, visual readouts of the images are more challenging than with  $^{11}\text{C}$ -PiB (Rowe and Villemagne 2011). While  $^{11}\text{C}$ -PiB PET images in subjects with AD pathology usually clearly show high radiotracer retention in the grey matter in excess of that in subjacent white matter, these novel  $^{18}\text{F}$  tracers frequently show loss of the normal grey-white matter demarcation as the predominant evidence of cortical A $\beta$  deposition (Rowe and Villemagne 2011).

To date, the vast majority of the A $\beta$  imaging literature is based on  $^{11}\text{C}$ -PiB studies, with studies using the first generation of fluorinated A $\beta$  radiotracers only recently being reported. The following survey of the state of the field is a reflection of this, and, unless otherwise specified, the reported results are from  $^{11}\text{C}$ -PiB studies.

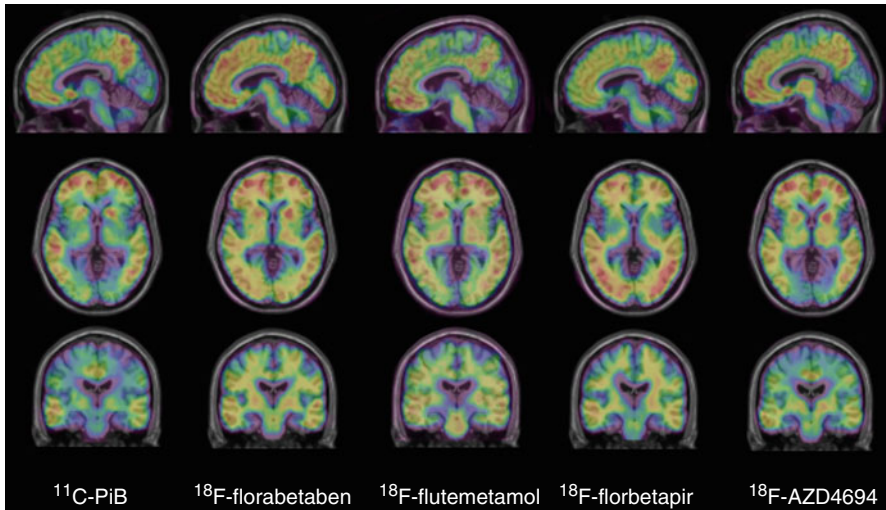
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### 10.3 A $\beta$ Imaging in Alzheimer's Disease

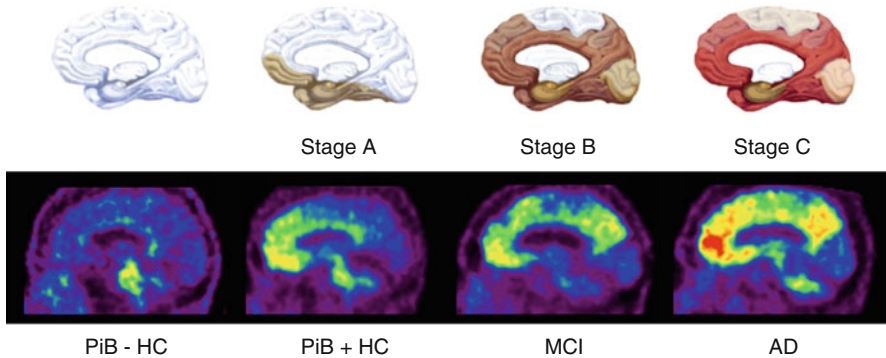
On visual inspection, cortical  $^{11}\text{C}$ -PiB retention is higher in AD, with a regional brain distribution that is highest in frontal, cingulate, precuneus, striatum, parietal and lateral temporal cortices, while occipital, sensorimotor and mesial temporal cortices are much less affected (Fig. 10.1). Both quantitative and visual assessments of PET images present a pattern of radiotracer retention that seems to replicate the sequence of A $\beta$  deposition found at autopsy (Braak and Braak 1997), with initial deposition in the orbitofrontal cortex, inferior temporal, cingulate gyrus and precuneus, followed by the remaining prefrontal cortex and lateral temporal and parietal cortices (Fig. 10.2). Multimodality studies in early AD have shown that the regional pattern of A $\beta$  deposition is similar to the anatomy of the 'default network' (Buckner et al. 2005; Sperling et al. 2009), a specific, anatomically defined brain system responsible for internal modes of cognition, such as self-reflection processes, conscious resting state or episodic memory retrieval (Buckner et al. 2008; Wermke et al. 2008), an association that is present even in non-demented subjects (Drzezga et al. 2011).

The regional distribution of  $^{11}\text{C}$ -PiB retention is not always the same and varies with the specific A $\beta$  distribution characteristic of the underlying pathology. For example, carriers of mutations associated with familial AD (Klunk et al. 2007; Koivunen et al. 2008b; Villemagne et al. 2009a), subjects with posterior cortical atrophy (Ng et al. 2007b; Tenovuo et al. 2008; Kambe et al. 2010; Formaglio et al. 2011) or CAA (Johnson et al. 2007; Dierksen et al. 2010) each presenting a different regional  $^{11}\text{C}$ -PiB distribution of retention to the one usually observed in sporadic AD (Klunk et al. 2004; Rowe et al. 2007).

Quantitative PET studies using diverse A $\beta$  radiotracers have shown a robust difference in retention between AD patients and age-matched controls (Klunk et al. 2004; Price et al. 2005; Mintun et al. 2006; Kudo et al. 2007; Pike et al. 2007;



**Fig. 10.1** Representative sagittal (*top row*), transaxial (*middle row*) and coronal (*bottom row*) PET images overlaid on MRI from Alzheimer's disease patients obtained with different A $\beta$  imaging radiotracers. From *left to right*,  $^{11}\text{C}$ -PiB,  $^{18}\text{F}$ -florbetaben,  $^{18}\text{F}$ -flutemetamol,  $^{18}\text{F}$ -florbetapir and  $^{18}\text{F}$ -AZD4694. The images show the typical pattern of tracer retention in AD, with the highest retention in frontal, temporal and posterior cingulate cortices, reflecting A $\beta$  plaque burden



**Fig. 10.2** *Top row*. Schematics showing the stages of A $\beta$  deposition in the human brain as proposed by Braak and Braak (1997). *Bottom row*. Representative sagittal PET images showing the regional brain distribution of  $^{11}\text{C}$ -PiB in two asymptomatic healthy age-matched controls, one with low (PiB - HC) and one with high A $\beta$  burden (PiB + HC), a subject classified as mild cognitive impairment (MCI) with significant A $\beta$  deposition in the brain and an Alzheimer's disease (AD) patient with even a higher A $\beta$  burden in the brain. The pattern of PiB retention replicates the sequence of A $\beta$  deposition described from postmortem studies (Braak and Braak 1997)

Rabinovici et al. 2007; Rowe et al. 2007, 2010; Jack et al. 2008a; Morris et al. 2009; Furst et al. 2012; Barthel et al. 2011; Fleisher et al. 2011; Villemagne et al. 2011a; Camus et al. 2012; Cselenyi et al. 2012).

Longitudinal studies with  $^{11}\text{C}$ -PiB are showing that significant, although small, increases in A $\beta$  deposition can be measured but also that these increases in A $\beta$  deposition are present in the whole spectrum of cognitive stages, from cognitively unimpaired individuals to AD dementia patients (Engler et al. 2006; Jack et al. 2009; Okello et al. 2009b; Resnick et al. 2010; Rinne et al. 2010; Sojkova et al. 2011b; Villemagne et al. 2011b; Villain et al. 2012). A $\beta$  accumulation is observed in individuals considered to have low A $\beta$  loads with about 7 % of them progressing above the threshold in about 2.5 years (Vlassenko et al. 2011). A $\beta$  accumulation is a slow process, and the evidence suggests that it remains constant in the preclinical and prodromal stages of the disease in those individuals deemed to have high A $\beta$  burdens while being slightly higher at the early stages of AD (Villemagne et al. 2011b). In individuals with the highest A $\beta$  burdens independent of clinical classification and also as Alzheimer's dementia progresses, the rates of A $\beta$  deposition start to slow down, although not completely reaching a plateau (Villain et al. 2012). This slower rate of A $\beta$  deposition associated with disease progression might be attributed to a saturation of the process or, more likely, extensive neuronal death that precludes A $\beta$  production.

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## 10.4 Antemortem and Postmortem Correlations

While clinicopathological studies have shown that the accuracy of clinical assessments for the diagnosis of AD ranges between 70 and 90 %, depending on the specialisation of the centre, the regional retention of  $^{11}\text{C}$ -PiB and the novel  $^{18}\text{F}$  radiotracers is highly correlated with regional A $\beta$  plaques as reported at autopsy or biopsy (Bacskaï et al. 2007; Ikonovic et al. 2008; Leinonen et al. 2008b; Villemagne et al. 2009b; Burack et al. 2010; Clark et al. 2011; Kadir et al. 2011; Sabbagh et al. 2011; Sojkova et al. 2011a; Wolk et al. 2011; Wong et al. 2013), with a higher A $\beta$  concentration in the frontal cortex than in hippocampus, consistent with previous reports (Arnold et al. 2000; Naslund et al. 2000). As mentioned before and in contrast with CSF studies, A $\beta$  imaging studies can assess both the quantity and regional brain distribution of A $\beta$ , as observed in the different patterns of regional distribution of A $\beta$  observed in sporadic AD (Klunk et al. 2004; Nordberg 2007), familial AD (Klunk et al. 2007; Koivunen et al. 2008b; Villemagne et al. 2009a), familial British dementia (Villemagne et al. 2010) and CAA subjects (Johnson et al. 2007; Dierksen et al. 2010). The results from A $\beta$  imaging might be considered for the brain regions to be sampled and stained for the neuropathological diagnosis of AD (Montine et al. 2012).

There have been a handful of cases reported with a discrepancy between a positive neuropathological finding or a strong biomarker profile of AD and a low PET signal. To date, only seven discrepant cases have been reported, three of them in mutation carriers (Tomiya et al. 2008; Schöll et al. 2011) and four in sporadic cases (Leinonen et al. 2008a; Cairns et al. 2009; Sojkova et al. 2011a; Ikonovic et al. 2012). No 'false-positive' cases have been reported. Tomiya and colleagues reported a case of a novel APP mutation (E693Delta) where the mutant A $\beta$  does not

fibrillise in the same way as wild-type A $\beta$  (Inayathullah and Teplow 2011) in which the  $^{11}\text{C}$ -PiB study showed low cortical retention (Tomiya et al. 2008). Schöll and colleagues report on two subject carriers of the Arctic APP mutation (Schöll et al. 2011). These two mutation carriers, while presenting with low  $^{11}\text{C}$ -PiB retention, had a clear ‘AD pattern’ of brain hypometabolism as measured by FDG, low A $\beta_{1-42}$  and elevated t-tau and p-tau in CSF (Schöll et al. 2011). While neuropathology was not available in these two subjects, a family member carrier of the same mutation presented with atypical plaque morphology—with ringlike plaques lacking a congophilic core—at autopsy (Basun et al. 2008). In regard to sporadic cases, Leinonen et al., while correlating  $^{11}\text{C}$ -PiB retention and frontal lobe A $\beta$  burden from biopsies on subjects undergoing intraventricular monitoring for normal pressure hydrocephalus, described a non-demented case with plaques that had a negative  $^{11}\text{C}$ -PiB scan (Leinonen et al. 2008a). Cairns et al. reported a longitudinally characterised subject with a low  $^{11}\text{C}$ -PiB scan that presented with evidence of cognitive decline and a CSF profile indicative of AD a year later (Cairns et al. 2009). At the time of autopsy, two and a half years after the  $^{11}\text{C}$ -PiB PET, diffuse A $\beta$  plaques were observed with only minimal neuritic plaques and NFT pathology. Sojkova et al. reported imaging-neuropathological correlations in five participants from the Baltimore Longitudinal Study of Aging (Sojkova et al. 2011a). While there was agreement in four subjects, even in one that had only sparse plaques at autopsy, a fifth presented with low global and regional  $^{11}\text{C}$ -PiB retention despite presenting moderate plaques at neuropathological examination and meeting CERAD criteria for ‘possible AD’ (Mirra et al. 1991). Ikonovic et al. (2012) reported autopsy findings in a subject with a clinical diagnosis of DLB and possible AD that presented with low  $^{11}\text{C}$ -PiB retention 17 months before death. At autopsy, focally frequent neocortical neuritic plaques fulfilled CERAD criteria of ‘definite AD’ (Mirra et al. 1991). Cortical A $\beta_{1-40}$  concentration levels were on the same range to those found in a typical AD case with high  $^{11}\text{C}$ -PiB retention, but A $\beta_{1-42}$  concentrations were lower. Furthermore, the majority of plaques labelled weakly with  $^{11}\text{C}$ -PiB and  $^3\text{H}$ -PiB binding were low, all findings suggesting low fibrillar A $\beta$ .

On the one hand, these cases illustrate the possibility that different conformations of A $\beta$  deposits (Levine and Walker 2010b) may affect the binding of tracers and that A $\beta$  imaging may not recognise all types of A $\beta$  pathologies with equal sensitivity (Walker et al. 2008; Rosen et al. 2011). On the other, it raises issues not only in regard to the sensitivity of A $\beta$  imaging (e.g. What is the minimal amount of A $\beta$  detected by PET?) but also in regard to the evaluation of brain tissue (e.g. type of antibodies used for immunohistochemistry and ELISA, fluorescent dyes, diagnostic criteria).

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## 10.5 A $\beta$ Deposition in Non-Demented Individuals and Its Relation with Cognition

About 25–35 % of elderly subjects performing within normal limits on cognitive tests present with high cortical  $^{11}\text{C}$ -PiB retention, predominantly in the prefrontal and posterior cingulate/precuneus regions (Mintun et al. 2006; Rowe et al. 2007,

2010; Aizenstein et al. 2008; Villemagne et al. 2008b; Mormino et al. 2009; Reiman et al. 2009b). These findings are in perfect agreement with postmortem reports that ~25 % of non-demented older individuals over the age of 75 have A $\beta$  plaques (Davies et al. 1988; Morris and Price 2001; Forman et al. 2007). A $\beta$  deposition in these non-demented individuals (Mintun et al. 2006; Rowe et al. 2007; Aizenstein et al. 2008; Villemagne et al. 2008b) might reflect preclinical AD (Price and Morris 1999). Furthermore, the prevalence of subjects with high <sup>11</sup>C-PiB retention increases each decade at the same rate as the reported prevalence of plaques in non-demented subjects in autopsy studies (Rowe et al. 2010). While cross-sectional examination of these controls essentially shows no significant differences in cognition (Mintun et al. 2006; Aizenstein et al. 2008; Jack et al. 2008a; Villemagne et al. 2008b; Rowe et al. 2010), significant cognitive differences in females were reported (Pike et al. 2011). More recently, Sperling and colleagues reported that high A $\beta$  deposition in the brain was correlated with lower immediate and delayed memory scores in otherwise healthy controls (Sperling et al. 2013). The detection of A $\beta$  pathology at the presymptomatic stage is of crucial importance because if this group truly represents preclinical AD (Price and Morris 1999; Thal et al. 2004; Backman et al. 2005; Small et al. 2007), it is precisely the group that may benefit the most from therapies aimed at reducing or eliminating A $\beta$  from the brain before irreversible neuronal or synaptic loss occurs (Sperling et al. 2011b).

Individuals fulfilling criteria for MCI are a heterogeneous group with a wide spectrum of underlying pathologies (Petersen 2000; Winblad et al. 2004). About 40–60 % of carefully characterised subjects with MCI will subsequently progress to meet criteria for AD over a 3–4-year period (Petersen et al. 1995, 1999; Petersen 2000). A $\beta$  imaging has proven useful in identifying MCI individuals with and without AD pathology. Approximately 50–70 % of the subjects classified as MCI present with high cortical <sup>11</sup>C-PiB retention (Price et al. 2005; Kempainen et al. 2007; Pike et al. 2007; Forsberg et al. 2008; Lowe et al. 2009; Mormino et al. 2009). While most studies found that subjects classified as non-amnesic MCI show low A $\beta$  levels in the brain (Pike et al. 2007; Lowe et al. 2009), other reports did not (Wolk et al. 2009). More specifically, subjects classified as non-amnesic single-domain MCI usually do not show A $\beta$  deposition, consistent with a non-AD underlying pathological process (Pike et al. 2007; Villemagne et al. 2011b).

To date, the relationship between A $\beta$  deposition and the development of clinical symptoms is not fully understood. Although A $\beta$  burden as assessed by PET does not correlate with measures of memory impairment in established clinical AD, it does correlate with memory impairment in MCI and healthy older subjects (Pike et al. 2007; Villemagne et al. 2008b). In subjects with MCI, this A $\beta$ -related impairment is thought to be mediated through hippocampal atrophy (Mormino et al. 2009) while modulated by cognitive reserve (Roe et al. 2008; Rentz et al. 2010) and glucose metabolism (Cohen et al. 2009), although at the AD stage there is no longer correlation between glucose metabolism, cognition and A $\beta$  burden (Furst et al. 2012).

Longitudinal studies are helping clarify the relationship between A $\beta$  burden and cognitive decline in healthy individuals and MCI subjects. High <sup>11</sup>C-PiB cortical retention in non-demented elderly subjects is associated with a greater risk of

cognitive decline (Villemagne et al. 2008b, 2011b; Resnick et al. 2010). For example, the evaluation of either the cognitive trajectories (Villemagne et al. 2008b; Resnick et al. 2010) or changes in cognition prospectively (Morris et al. 2009; Villemagne et al. 2011b; Doraiswamy et al. 2012) shows that individuals with substantial A $\beta$  deposition are more likely to present with cognitive decline. Aggregating the results from recently reported longitudinal studies reveals that 65 % of MCI subjects with marked <sup>11</sup>C-PiB retention progressed to AD over 2–3 years, showing that MCI subjects with high A $\beta$  deposition in the brain are >10 times more likely to progress to AD than those with low A $\beta$  deposition, highlighting the clinical relevance and potential impact in patient management of A $\beta$  imaging (Forsberg et al. 2008; Okello et al. 2009b; Wolk et al. 2009; Villemagne et al. 2011b). The observations that <sup>11</sup>C-PiB retention in non-demented individuals relates to episodic memory impairment, one of the earliest clinical symptoms of AD, and that extensive A $\beta$  deposition is associated with a significant higher risk of cognitive decline in HC and with progression from MCI to AD emphasise the non-benign nature of A $\beta$  deposition and support the hypothesis that A $\beta$  deposition occurs well before the onset of symptoms, further suggesting that early disease-specific therapeutic intervention at the presymptomatic stage might be the most promising approach to either delay onset or halt disease progression (Sperling et al. 2011b).

The high prevalence of A $\beta$  deposition in non-demented individuals raises questions in regard to A $\beta$  toxicity and deposition. The evidence points to the fact that A $\beta$  toxicity in the form of oligomers and A $\beta$  deposition in the form of aggregates precede by many years the appearance of clinical symptoms (Price and Morris 1999). These neurotoxic processes eventually lead to synaptic and neuronal dysfunction, manifested as cognitive impairment, grey matter atrophy and glucose hypometabolism (Eckert et al. 2003; Suo et al. 2004; Leuner et al. 2007). Therefore, it is highly likely that <sup>11</sup>C-PiB retention in non-demented individuals reflects preclinical AD (Mintun et al. 2006; Rowe et al. 2007; Aizenstein et al. 2008; Villemagne et al. 2008b). This may be associated or attributed to a different susceptibility/vulnerability to A $\beta$ , at either a cellular (frontal neurons seems to be more resistant to A $\beta$  than hippocampal neurons) (Roder et al. 2003; Resende et al. 2007), a regional (compensatory upregulation of choline acetyltransferase (ChAT) activity in the frontal cortex and hippocampi of MCI and early AD subjects) (DeKosky et al. 2002) as well as at an individual or personal level, either due to a particular cognitive reserve (Mortimer 1997; Stern 2002; Kemppainen et al. 2008; Roe et al. 2008), differences in A $\beta$  conformation affecting toxicity and/or aggregation (Lockhart et al. 2005; Deshpande et al. 2006; Levine and Walker 2010a; Walker et al. 2008), or because an idiosyncratic threshold must be exceeded for synaptic failure and neuronal death to ensue (Suo et al. 2004). These factors would help explain why some older individuals with a significant A $\beta$  burden are cognitively unimpaired, while others with lower A $\beta$  burden and no genetic predisposing factors have already developed the full clinical AD phenotype. Ongoing longitudinal studies will help identify those subjects that despite substantial A $\beta$  deposition do not develop the AD phenotype, thus allowing to isolate genetic or environmental factors that may convey resistance to A $\beta$  (Sojkova and Resnick 2011).

The lack of a strong association between A $\beta$  deposition and measures of cognition, synaptic activity and neurodegeneration in AD, in addition to the evidence of A $\beta$  deposition in a high percentage of MCI and asymptomatic HC, suggests that A $\beta$  is an early and necessary, though not sufficient, cause for cognitive decline in AD (Villemagne et al. 2008b; Rabinovici et al. 2010; Sojkova and Resnick 2011), indicating the involvement of other downstream mechanisms, likely triggered by A $\beta$  such as NFT formation, synaptic failure and eventually neuronal loss. Also at play are factors as age, years of education, occupational level and brain volume among others that, under the umbrella of 'cognitive reserve', appear to have a modulatory role between cognition and A $\beta$  deposition (Roe et al. 2008; Chetelat et al. 2010b; Tucker and Stern 2011). Perhaps specific in vivo tau imaging will help elucidate or bridge the gap between A $\beta$  deposition and the persistent decline in cognitive function observed in AD (Fodero-Tavoletti et al. 2011; Villemagne et al. 2012a).

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## 10.6 Relationship of A $\beta$ Imaging with Other Biomarkers

Another rapidly growing area is the exploration of the potential association between biomarkers of A $\beta$  deposition or neurodegeneration (Wahlund and Blennow 2003; Morris et al. 2005; Sunderland et al. 2005; de Leon et al. 2006; Thal et al. 2006; Blennow et al. 2007; Shaw et al. 2007; Clark et al. 2008; Jack et al. 2010; Albert et al. 2011; McKhann et al. 2011; Storandt et al. 2012) and A $\beta$  burden as measured by PET (Jack et al. 2008a, 2010).

### 10.6.1 FDG

While the typical pattern of A $\beta$  deposition in sporadic AD is highest in frontal, cingulate, precuneus, striatum, parietal and lateral temporal cortices (Klunk et al. 2004), in FDG studies, the typical 'AD pattern' is of temporoparietal and posterior cingulate hypometabolism with sparing of the basal ganglia, thalamus, cerebellum and primary sensorimotor cortex (Salmon et al. 1994; Devanand et al. 1997; Coleman 2005; Jagust et al. 2007). Due to its high sensitivity (>90 %) for detecting temporoparietal and posterior cingulate hypometabolism, FDG-PET has improved diagnostic and prognostic accuracy in patients with probable AD (Salmon et al. 1994; Kennedy et al. 1995; Small et al. 1995; Silverman et al. 2001, 2002). A similar pattern of hypometabolism has been reported in normal elderly ApoE  $\epsilon$ 4 carriers (Reiman et al. 1996), MCI (Chetelat et al. 2003, 2005; Mosconi et al. 2006a), asymptomatic subjects with mutations associated with familial AD (Kennedy et al. 1995; Rossor et al. 1996) and subjects with a strong family history of AD (Mosconi et al. 2006b). FDG hypometabolism is correlated with cognition (Landau et al. 2011; Furst et al. 2012) and is predictive of future cognitive decline (Drzezga et al. 2003, 2005; Mosconi et al. 2004).

Visual assessment of PET images by clinicians blinded to the clinical status has demonstrated that  $^{11}\text{C}$ -PiB was more accurate than FDG to distinguish AD from HC

(Ng et al. 2007a) and slightly better than FDG in differentiating AD from FTLD (Rabinovici et al. 2011). Similarly, A $\beta$  imaging outperforms FDG at identifying MCI subtypes (Lowe et al. 2009).

While some reports found no association between FDG and  $^{11}\text{C}$ -PiB in AD (Furst et al. 2012), others found an inverse correlation between them in temporal and parietal cortices (Cohen et al. 2009), but no correlation has been shown in the frontal lobe (Klunk et al. 2004; Edison et al. 2007). A possible explanation for this dissociation is that there is a compensatory mechanism such as upregulation of ChAT in the frontal lobe of MCI individuals and mild AD patients (DeKosky et al. 2002; Ikonomic et al. 2007) that might delay the manifestation of synaptic dysfunction; therefore, no hypometabolism is observed on FDG in the frontal lobe. Glucose metabolism in the frontal lobe eventually decreases as the disease progresses, and the characteristic temporoparietal pattern of AD becomes less apparent (Mielke et al. 1992; Herholz 1995). Conversely to what is observed in the frontal area, in AD patients, ChAT is significantly decreased in the posterior cingulate gyrus (Ikonomic et al. 2011), which is characterised by being one of the regions where marked and early A $\beta$  deposition is associated with substantial hypometabolism (Drzezga et al. 2011; Yokokura et al. 2011).

### 10.6.2 CSF

Analysis of CSF allows simultaneous measurement of the concentration of the two main hallmarks of AD, A $\beta$  and tau. It has been reported to be highly accurate in the diagnosis of AD as well of predicting cognitive decline (Blennow et al. 2007; de Leon et al. 2007; Hansson et al. 2007; Mattsson et al. 2009, 2011). The typical CSF profile in AD is low A $\beta_{1-42}$  and high total (t-tau) and phosphorylated tau (p-tau) (Strozyk et al. 2003; Hampel et al. 2010). Slower A $\beta$  clearance from the brain (Bateman et al. 2006; Mawuenyega et al. 2010) is likely to lead to A $\beta$  deposition in the brain and lower CSF A $\beta_{1-42}$  concentrations. While there is no correlation between  $^{11}\text{C}$ -PiB retention and CSF t-tau or p-tau (Tolboom et al. 2009a; Forsberg et al. 2010), several studies have reported a strong inverse correlation between A $\beta$  deposition in the brain as measured by  $^{11}\text{C}$ -PiB and CSF A $\beta_{1-42}$  (Fagan et al. 2006, 2007, 2009; Forsberg et al. 2008; Koivunen et al. 2008a; Grimmer et al. 2009). Both high  $^{11}\text{C}$ -PiB retention and low CSF A $\beta_{1-42}$  have been observed in cognitively unimpaired individuals probably reflecting A $\beta$  deposition years before the manifestation of the AD phenotype (Mintun et al. 2006; Fagan et al. 2007, 2009; Rowe et al. 2007; Aizenstein et al. 2008). Large population studies such as ADNI (Shaw et al. 2007; Apostolova et al. 2010) will further validate the value of A $\beta$  imaging and CSF assessments as antecedent biomarkers of AD.

### 10.6.3 MRI

While A $\beta$  imaging or CSF A $\beta$  provides information in regard to A $\beta$  pathology, CSF tau quantification, FDG and structural MRI provide information related to the



neurodegenerative process (Jack et al. 2010). Hippocampal and cortical grey matter atrophy along with ventricular enlargement are typical MRI findings in AD and MCI (Frisoni et al. 2010; Drago et al. 2011). Furthermore, it has been shown that the rates of hippocampal atrophy might be predictive of conversion from MCI to AD (Jack et al. 2008b).

A $\beta$  deposition is associated with regional cerebral atrophy as measured by MRI (Archer et al. 2006; Bourgeat et al. 2010; Chetelat et al. 2010a; Becker et al. 2011) and correlates with the rates of cerebral atrophy (Becker et al. 2011; Tosun et al. 2011). Moreover, the data suggest that the relationship between A $\beta$  deposition and cortical atrophy is sequential, where A $\beta$  deposition precedes synaptic dysfunction and neuronal loss (Chetelat et al. 2010a; Drzezga et al. 2011; Forster et al. 2012), then manifested as structural changes (Becker et al. 2011). While one report did not find a correlation between atrophy trajectories and <sup>11</sup>C-PiB retention in cognitively unimpaired elderly individuals (Driscoll et al. 2011), another reported that those with high A $\beta$  deposition showed a significantly higher rate of atrophy in the temporal and posterior cingulate cortices compared to those with low A $\beta$  burden (Chetelat et al. 2012).

#### 10.6.4 Neuroinflammation

Microglia are the primary resident immune surveillance cells in the brain and are thought to play a significant role in the pathogenesis of several neurodegenerative disorders including AD (Venneti et al. 2006). Activated microglia can be measured using radioligands for the translocator protein (TSPO), formerly known as the peripheral benzodiazepine receptor. The TSPO is upregulated on activated macrophages and microglia and has been established as a biomarker of neuroinflammation in the central nervous system. Most reports found that in AD there is no association between A $\beta$  deposition and microglial activation measured by [<sup>11</sup>C]PK11195 (Edison et al. 2008a; Okello et al. 2009a; Wiley et al. 2009) despite being an association between [<sup>11</sup>C]PK11195 binding and both glucose hypometabolism and severity of dementia (Edison et al. 2008a; Yokokura et al. 2011). More recently, PET studies assessing the relationship between A $\beta$  deposition and neuroinflammation have been proposed using the MAO-B inhibitor L-deprenyl as a marker for astrocytosis (Carter et al. 2012).

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### 10.7 Relationship of A $\beta$ Deposition with Genetic Risks and Predisposing Factors

Age is the strongest risk factor in sporadic AD, with the prevalence of the disease increasing exponentially with age. These risks are increased in the presence of the ApoE  $\epsilon$ 4 allele (Farrer et al. 1997). Both risk factors have been directly associated with A $\beta$  burden as measured by PET (Reiman et al. 2009b; Morris et al. 2010; Rowe et al. 2010).

To date, ApoE  $\epsilon$ 4 is the most consistent genetic risk factor associated with sporadic AD, and its presence has been associated with an earlier age of onset and a dose-dependent—either one or two ApoE  $\epsilon$ 4 alleles—higher risk of developing AD

(Farrer et al. 1997). Examination of ApoE  $\epsilon$ 4 allele status revealed that, independent of clinical classification,  $\epsilon$ 4 carriers present with significantly higher  $^{11}\text{C}$ -PiB retention than non- $\epsilon$ 4 carriers, further emphasising the crucial role that ApoE plays in the metabolism of A $\beta$  (Reiman et al. 2009b; Morris et al. 2010; Rowe et al. 2010). When specific clinical groups are examined, the results—from both autopsy and A $\beta$  imaging studies—are not that clear cut. While some studies found significant differences in A $\beta$  burden between AD  $\epsilon$ 4 carriers and non- $\epsilon$ 4 carriers (Gomez-Isla et al. 1996; Drzezga et al. 2008; Grimmer et al. 2010), others did not (Berg et al. 1998; Klunk et al. 2004; Rowe et al. 2007; Rabinovici et al. 2010).

Both symptomatic and asymptomatic individual carriers of mutations within the APP or presenilin 1 or 2 genes associated with familial AD present with very high and early  $^{11}\text{C}$ -PiB retention in the caudate nuclei, retention that seems to be independent of mutation type or disease severity (Klunk et al. 2007; Koivunen et al. 2008b; Remes et al. 2008; Villemagne et al. 2009a). Larger multicenter studies are helping elucidate the value of several biomarkers in these autosomal mutation carriers, assessment that might lead to better targeted disease-specific therapeutic strategies (Bateman et al. 2012).

While a similar pattern of A $\beta$  deposition as seen in AD has been reported in older adults with Down syndrome (Landt et al. 2011), a completely different pattern of  $^{11}\text{C}$ -PiB retention was observed in a mutation carrier of familial British dementia (Villemagne et al. 2010).

There are several other factors that have been associated with AD. Among these, the most relevant are vascular risk factors (VRF), such as diabetes, hypercholesterolemia, hypertension and hyperhomocysteinemia. The influence of these VRF on AD pathology is an area that, despite the long and intense scientific debate, has not been clearly established (Viswanathan et al. 2009). While some studies support a direct role of VRF in the development of AD (Qiu et al. 2010), others suggest that they may accelerate its clinical presentation (Riekse et al. 2004). Recent studies have used MRI white matter hyperintense lesions as surrogate markers of vascular disease in association with assessment of A $\beta$  deposition and cognition (Kuczynski et al. 2008; Marchant et al. 2012).

As with AD, VRF are strongly age-dependent factors that share similar pathogenic pathways, such as oxidative stress or inflammation, so it is not easy to extricate one from the other in order to ascertain a causal, casual or co-morbid association between them (Rosendorff et al. 2007). On the other hand, in light of the absence of disease-modifying therapies for AD, the relevance of these risk factors rests in the fact that early intervention over them, especially at middle age, might have an impact on either the onset or progression of AD.

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## 10.8 A $\beta$ Imaging in Other Neurodegenerative Conditions

A $\beta$  imaging in a wide spectrum of neurodegenerative conditions has yielded diverse results. Although lower than in AD, similar patterns of  $^{11}\text{C}$ -PiB retention are usually observed in DLB (Rowe et al. 2007; Gomperts et al. 2008; Maetzler

et al. 2009). Cortical  $^{11}\text{C}$ -PiB retention is also higher in subjects diagnosed with CAA (Johnson et al. 2007), while there is usually no cortical  $^{11}\text{C}$ -PiB retention in patients with FTLN (Rabinovici et al. 2007; Rowe et al. 2007; Drzezga et al. 2008; Engler et al. 2008). A $\beta$  imaging has also facilitated differential diagnosis in cases of patients with atypical presentations of dementia (Ng et al. 2007b; Wolk et al. 2012a).

### 10.8.1 Cerebral Amyloid Angiopathy

CAA, characterised by A $\beta$  deposits in and around the media of small arteries and arterioles of the cerebral cortex and leptomeninges, has been found to be present in most patients with AD (Jellinger and Attems 2005). To this date, neuropathological examination of the brain remains the only definitive method for diagnostic confirmation of CAA. However, the combination of A $\beta$  imaging with  $^{11}\text{C}$ -PiB PET and T2\* susceptibility-weighted (SWI) MR imaging (Knudsen et al. 2001) allows for the concomitant assessment of molecular and structural changes in vivo. The combination of cerebral microhaemorrhages (MH) and superficial siderosis (SS) has been suggested as radiological markers for CAA (Feldman et al. 2008). A $\beta$  imaging studies have shown both processes may be intimately associated with A $\beta$  deposition (Dierksen et al. 2010; Dhollander et al. 2011), preferentially in posterior areas of the brain, showing a distinct pattern of  $^{11}\text{C}$ -PiB retention than the one observed in sporadic AD (Johnson et al. 2007). Furthermore, focal A $\beta$  deposition might be useful in predicting new MH in CAA patients (Gurol et al. 2012). While deep subcortical MH are generally associated with VRF, lobar MH (particularly posterior) (Pettersen et al. 2008) are usually attributed to CAA (Knudsen et al. 2001; Vernooij et al. 2008). Lobar MH are a frequent finding in AD patients or even in cognitively normal older individuals, and they are strongly associated with increasing age and A $\beta$  deposition (Yates et al. 2011). This association between A $\beta$  and vascular lesions has crucial implications not only for the selection and risk stratification of individuals undergoing anticoagulant therapies but also in those enrolled in anti-A $\beta$  therapeutic trials (Weller et al. 2009).

### 10.8.2 Lewy Body Diseases

While AD is the most common cause of dementia in the elderly, DLB accounts for 20 % of the cases (McKeith et al. 2005). The pathological hallmark of DLB is the presence of  $\alpha$ -synuclein-containing LB within the neocortical and limbic regions (McKeith et al. 2005), as well as substantial loss of pigmented dopaminergic neurons in the substantia nigra, reflected in a marked dopaminergic terminal denervation in the striatum (McKeith and Mosimann 2004). More refined neuropathological techniques have revealed extensive synaptic deposits of  $\alpha$ -synuclein, more concordant with the DLB clinical phenotype than the usually sparse cortical LB (Schulz-Schaeffer 2010). Overlap of cognitive symptoms early in the disease

course offers a challenge for clinicians making it difficult to distinguish between patients that will develop AD versus those that will ultimately develop DLB. Postmortem histopathological studies have identified that 50–80 % of DLB cases often have cortical A $\beta$  deposits with characteristics and a distribution similar to AD patients (McKeith et al. 2005; Rowe et al. 2007; Edison et al. 2008b). This has also been described as ‘mixed’ DLB/AD or ‘Lewy body variant of AD’. The so-called ‘pure’ DLB is much less common, and it is not clear if the clinical characteristics and prognosis differ from the mixed-pathology cases. On visual inspection, cortical <sup>11</sup>C-PiB retention in DLB is generally lower and more variable than in AD, probably reflecting a larger spectrum of A $\beta$  deposition (Rowe et al. 2007; Gomperts et al. 2008; Maetzler et al. 2009). Therefore, A $\beta$  imaging is not a useful tool in differentiating between AD and DLB but might assist in the differential diagnosis of those cases (‘pure’ DLB) without A $\beta$  deposition in the brain (Armstrong et al. 2000).

Taking advantage of its high affinity for  $\alpha$ -synuclein (Fodero-Tavoletti et al. 2009a), <sup>11</sup>C-BF-227 has been used for the assessment of multiple system atrophy (MSA), a disease characterised by the glial accumulation of  $\alpha$ -synuclein in the absence of A $\beta$  plaques, showing a higher retention in MSA patients compared to age-matched controls (Kikuchi et al. 2010). Interestingly, while <sup>11</sup>C-BF-227 retention in DLB patients was lower compared to AD in most cortical regions, DLB presented with significantly higher <sup>11</sup>C-BF-227 retention in the amygdala (Furukawa et al. 2011).

In contrast to A $\beta$  imaging, assessing the integrity of dopaminergic terminals via dopamine transporter (DAT) or vesicular monoamine transporter type 2 (VMAT2) imaging can robustly detect reductions of dopaminergic nigrostriatal afferents in DLB patients, assisting in the differential diagnosis from AD (O’Brien et al. 2004; Koeppe et al. 2008; Villemagne et al. 2012d).

Cortical A $\beta$  is not usually present in cognitively intact Parkinson’s disease (PD) patients, and no significant <sup>11</sup>C-PiB cortical retention is usually observed in these patients (Johansson et al. 2008). A $\beta$  deposits, both vascular and parenchymal, are frequent, however, in PD patients who develop dementia (PDD) (Edison et al. 2008b; Gomperts et al. 2008; Maetzler et al. 2008, 2009; Burack et al. 2010; Foster et al. 2010; Kalaitzakis et al. 2011).

The contribution of A $\beta$  to the development of Lewy body diseases remains unclear, but cortical A $\beta$  deposits are associated with extensive  $\alpha$ -synuclein lesions and higher levels of insoluble  $\alpha$ -synuclein lesions (Pletnikova et al. 2005), as well as exacerbation of neuronal injury (Masliah et al. 2001). Furthermore, it has been shown that in PD, CSF A $\beta$  is predictive of cognitive decline (Siderowf et al. 2010). Along these lines, while A $\beta$  imaging cannot contribute to the differential diagnosis between AD and DLB, it may have prognostic relevance in these Lewy body diseases. For example, similar to what has been reported for PDD, where higher A $\beta$  burden was associated with a shorter prodromal phase before dementia (Halliday et al. 2008), A $\beta$  burden in DLB patients was inversely correlated with the interval from onset of cognitive impairment to the full development of the DLB phenotype (Rowe et al. 2007).

### 10.8.3 Frontotemporal Lobar Degeneration

FTLD is a syndrome that can also be clinically difficult to distinguish from early-onset AD, especially at the initial stages of the disease. Based on clinical phenotype, FTLD has been categorised mainly into two classes: behavioural variant of FTLD (bvFTLD) with distinct changes in behaviour and personality with little effect on language functions and progressive aphasia (comprised by semantic dementia (SD), progressive non-fluent aphasia (PNFA) and logopenic aphasia (LPA)) showing progressive language deficits, with less obvious personality and behavioural changes (Rabinovici and Miller 2010).

A $\beta$  deposition is not a pathological trait of FTLD, and definitive differential diagnosis can only be established after postmortem examination of the human brain. Neuropathological examination of the brain in FTLD shows variable frontal and temporal atrophy (Cairns et al. 2007; Hodges and Patterson 2007; Snowden et al. 2007), microvacuolation and neuronal loss, with white matter myelin loss, astrocytic gliosis as well as neuronal and glial inclusions (Cairns et al. 2007). Three intraneuronal inclusion types have been identified in FTLD: (1) hyperphosphorylated tau (FTLD tau), (2) ubiquitin hyperphosphorylated and proteolysed TAR-DNA-binding protein 43 (FTLD-TDP-43) and (3) fused in sarcoma (FUS) positive (Taniguchi et al. 2004; Mott et al. 2005; Neumann et al. 2006, 2009). Tau-positive inclusions account for approximately 40 % of all FTLD cases, the remainder being tau negative and TDP-43/ubiquitin positive (Josephs et al. 2004). In bvFTLD, both tau and TDP-43 are equally prevalent; and while 90 % of the SD cases show TDP-43 pathology, PNFA presents predominantly (70 %) tau pathology (Josephs et al. 2004; Mackenzie et al. 2008). In contrast, LPA is thought to be a language presentation of AD, with typical A $\beta$  and NFT (Leyton et al. 2011).

A $\beta$  imaging has been helpful in the differential diagnosis between FTLD and AD (Rabinovici et al. 2007; Rowe et al. 2007; Drzezga et al. 2008; Engler et al. 2008). Furthermore, A $\beta$  imaging has been used to ascertain the absence of AD pathology in the different FTLD aphasias (Drzezga et al. 2008; Rabinovici et al. 2008; Leyton et al. 2011). Despite displaying similar specificities, the diagnostic performance of A $\beta$  imaging proved to be more sensitive for the diagnosis of FTLD than FDG (Rabinovici et al. 2011).

### 10.8.4 Prion Diseases

No cortical  $^{11}\text{C}$ -PiB retention was observed in sporadic Creutzfeldt-Jakob disease (CJD) cases (Villemagne et al. 2009b). Due to the rapid progression and relatively short duration of symptomatic illness, sporadic CJD patients do not demonstrate appreciable PrP-plaque deposition at autopsy (Liberski 2004). Although some sporadic CJD molecular subtypes can manifest larger PrP plaques (Hill et al. 2003), the most common subtype usually demonstrates only very fine 'synaptic' and small perivacuolar deposits (Hill et al. 2003; Liberski 2004). A preliminary study in transmissible spongiform encephalopathies showed that A $\beta$  imaging with  $^{11}\text{C}$ -BF-227

might be able to distinguish between Gerstmann-Straussler-Scheinker disease (GSS) and sporadic CJD disease with clear tracer retention in brain regions of PrP deposition (Okamura et al. 2010).

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## 10.9 A $\beta$ Imaging in the Development of Disease-Specific Therapeutics

A $\beta$  imaging with PET is also contributing to the development of more effective therapies by allowing better selection of patients for anti-A $\beta$  therapy trials and providing a means to measure their impact on A $\beta$  burden (Rinne et al. 2010; Ostrowitzki et al. 2012). While these studies represent one of the principal applications of A $\beta$  imaging, they have brought forward an issue that needs to be addressed, namely, that the advent of novel A $\beta$  tracers with differing pharmacological and pharmacokinetics properties, summed to the diverse arsenal of quantitative approaches, and contrasting criteria for the selection of internal scaling region pose a challenge when trying to compare results from therapeutic trials that use different A $\beta$  tracers or quantitative tools.

The contribution of A $\beta$  imaging to the selection of patients for therapeutic trials needs to be complemented with adequate MRI sequences such as SWI or GRE for the detection of vascular pathology to rule out the possibility of vascular complications such as amyloid-related imaging abnormalities (ARIA), either as ‘vasogenic edema’ and/or sulcal effusion (ARIA-E) or as hemosiderin deposits including MH and SS (ARIA-H) (Cordonnier 2010; Sperling et al. 2011c). The presence of MH is impacting on patient selection in therapeutic trials, and some anti-A $\beta$  immunotherapy trials are already excluding individuals with MH. To make matters worse, about one third of non-demented individuals with high A $\beta$  burden and no prior history of cerebrovascular disease showed MH (Yates et al. 2011). While focal A $\beta$  deposition might be a better predictor of a vascular event (Gurol et al. 2012), only longitudinal follow-up of large cohorts of patients will allow elucidation of the relevant risk factors for lobar MH.

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### 10.10 Pending Issues

There are still some pending issues in regard to A $\beta$  imaging; some are clinically relevant, while others remain in the realm of research settings.

One of the issues is in regard to the utility of a cut-off given the continuous spectrum of A $\beta$  deposition (Jagust 2011; Mormino et al. 2012). In order to adopt a specific threshold, it needs to be shown that this threshold is relevant and accurate from both a diagnostic and prognostic point of view. From a clinical point of view, a visual binary read will help separate those with a significant A $\beta$  burden in the brain from those with a null or low A $\beta$  burden. But some questions arise: What is really a ‘negative’ scan? What is the clinical relevance of focal A $\beta$  deposition? What is the weight to be attributed to this focal A $\beta$  deposition given the known functional and/or structural regional susceptibility such as the one observed in the posterior

cingulate (Drzezga et al. 2011) and orbitofrontal cortices (Resnick et al. 2007)? Similar dilemmas arise in research settings. For example, is someone with a  $^{11}\text{C}$ -PiB SUVR of 1.44 really 'negative' for A $\beta$  because it is below a 1.50 SUVR threshold? In order to avoid being trapped in this dichotomy, some researchers use tertiles (Resnick et al. 2010), while others, like Prof. Klunk, are proposing to distinguish two thresholds for 'positivity', one more sensitive to detect significant A $\beta$  deposition usually in still cognitively unimpaired elderly individuals and another higher one that can be more specifically ascribe the clinical phenotype of dementia to A $\beta$  pathology (Klunk et al. 2012). In addition to establishing a clinically relevant threshold, there is a need to change the nomenclature employed to distinguish this binary partition. The terms 'positive' and 'negative' have denotations, connotations and implications that might be, in the long run, prejudicial for the field. Given the potentially misleading positive connotations of a 'negative' scan, it might be more appropriate to use the term 'low', while instead of using 'positive' it might be more accurate to use 'high', the same way other risk factors such as blood pressure or cholesterol are described in clinical settings.

Other issues are related to the choice of reference region. This matter is further complicated by the introduction of novel A $\beta$  radiotracers with physicochemical and pharmacokinetic features somewhat different from  $^{11}\text{C}$ -PiB that benefit from different approaches in the sampling and selection of the reference region. For example, studies with  $^{18}\text{F}$ -florbetapir tend to use the whole cerebellum (Clark et al. 2011), while using the pons as reference region seems to reduce variability for  $^{18}\text{F}$ -flutemetamol (Vandenberghe et al. 2010a). Closely related to the choice and sampling of the reference region are issues referring to the quantitative or semi-quantitative approaches used to determine A $\beta$  burden. Given that the studies are performed in individuals or populations who might not tolerate long scanning sessions, the majority of studies use a short 20- or 30-min PET scan at apparent steady state (Lopresti et al. 2005). While all the novel F-18 A $\beta$  tracers have a somewhat fixed time window for optimal scanning (40–50 min postinjection for  $^{18}\text{F}$ -florbetapir and  $^{18}\text{F}$ -AZD4694 and about 90 min for  $^{18}\text{F}$ -florbetaben and  $^{18}\text{F}$ -flutemetamol), several intervals (40–60, 40–70, 50–70 or 60–90 min postinjection) have been used with  $^{11}\text{C}$ -PiB (Lopresti et al. 2005; Rowe et al. 2007; Yee et al. 2007; Edison et al. 2008b). While these image acquisition intervals are more than enough to obtain clinically useful images, are they adequate to reliably establish A $\beta$  burden in longitudinal studies or therapeutic trials? (Rinne et al. 2010; Ostrowitzki et al. 2012; Ossenkoppele et al. 2012). Is arterial blood sampling required? Is a simple ratio enough, or is a full compartmental analysis needed? (Lopresti et al. 2005; Price et al. 2005). If different A $\beta$  imaging tracers are used and/or different quantification approaches are applied (use of either BP or SUVR, as well as choice of reference region), in between tracer equivalence or standards must be established for the interpretation and comparison of efficacy in therapeutic trials. Finally, the issue of partial volume correction (PVC) raises several other questions: How much of the intrinsic noise of the PET signal is augmented by PVC? Can longitudinal studies be evaluated without PVC (Jack et al. 2009; Villemagne et al. 2011b)? How to correct for spillover radioactivity from white matter? All these issues remain contentious.

Finally, and given that there is no cure for AD, diagnosing the presence or absence of AD pathology *in vivo* raises ethical issues. While the presence of AD pathology has undoubtedly been associated with a significantly greater risk of cognitive decline, there is still not enough longitudinal data available to attach a firm prognostic clinical significance to a 'positive' scan. While this is clearer in subjects classified as MCI, it is still controversial in cognitively unimpaired individuals. At this stage, A $\beta$  imaging, in combination with other modalities, is probably the best diagnostic tool to rule out A $\beta$  pathology in cognitively impaired individuals being evaluated for cognitive decline. The available data clearly show that A $\beta$  production and deposition are not benign processes with a more prominent role at the early, mostly asymptomatic, stages of the disease (Hyman 2011; Karran et al. 2011); therefore, anti-A $\beta$  therapy at these stages seems a logical approach (Sperling et al. 2011b). On the other hand, we still do not have the full grasp of the long-term cognitive consequences of A $\beta$  deposition. Longitudinal A $\beta$  imaging, especially of cognitively unimpaired elderly individuals, is allowing the assessment of pathology almost simultaneously with cognition and other biomarkers of neurodegeneration. This will provide not only a better picture of how these different factors interact but also the weight or relevance this complementary and/or supplementary information plays at different stages of the disease.

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## 10.11 CODA

The clinical diagnosis of AD is typically based on progressive cognitive impairments while excluding other diseases. Clinical diagnosis of sporadic disease is challenging, however, often presenting mild and nonspecific symptoms attributable to diverse and overlapping pathology presenting similar phenotypes. Overall, the accuracy of clinical diagnosis of AD compared to neuropathological examination ranges between 70 and 90 % (Beach et al. 2012). While clinical criteria, together with current structural neuroimaging techniques (CT or MRI), are sufficiently sensitive and specific for the diagnosis of AD at the mid to late stages of the disease, they are focused on relatively nonspecific features such as memory and functional activity decline or brain atrophy that are late features in the course of the disease. Confirmation of diagnosis of AD still relies on autopsy. But how reliable is pathology? How much of a 'gold standard' is autopsy? (Jellinger 2010; Scheltens and Rockwood 2011). A more sensible paradigm, adopting a more fluid model that integrates all cognitive, biochemical and imaging biomarkers that can provide a better predictive framework, has been proposed in the new diagnostic criteria for AD (Dubois et al. 2010; Sperling and Johnson 2010; McKhann et al. 2011), MCI (Albert et al. 2011) and preclinical AD (Sperling et al. 2011a). Along the same lines, Scheltens and Rockwood suggest that 'a shift in focus from why people with AD have plaques and tangles to why not all people with plaques and tangles have AD would be welcome' (Scheltens and Rockwood 2011). While most people with AD pathology develop AD dementia, there are some that while having the pathology do not. What makes them different? What conveys resistance to some or,



conversely, what makes others more vulnerable to the same pathological burden? Identifying these factors will allow a more discerning selection of individuals that will benefit from early intervention with anti-A $\beta$  medication while also providing insights into potential preventive strategies or even new therapeutic approaches (Sojkova and Resnick 2011; Sperling et al. 2011b). While the new diagnostic criteria have blurred once again the boundaries between MCI and AD (Morris 2012), it also allows for earlier diagnosis and therapeutic intervention, arguing that when there is a clear history of progressive cognitive decline, objective evidence from psychometric tests of episodic memory impairment and characteristic abnormalities in the CSF and/or neuroimaging studies such as A $\beta$  imaging, dementia might not be required for the diagnosis of probable AD (Dubois et al. 2010; Sperling and Johnson 2010; McKhann et al. 2011). Thus, as the criteria for the diagnosis of AD change, A $\beta$  imaging is likely to play an increasingly important role in clinical practice provided it is accessible and affordable (Villemagne and Rowe 2010).

The pathological process usually begins decades before symptoms are evident, making early identification difficult. This in turn precludes early intervention with disease-modifying medications during the presymptomatic period, which by arresting neuronal loss would presumably achieve the maximum benefits of such therapies (Villemagne et al. 2008a). Therefore, a change in the diagnostic paradigm is warranted, where diagnosis moves away from identification of signs and symptoms of neuronal failure—indicating that central compensatory mechanisms have been exhausted and extensive synaptic and neuronal damage is present—to the noninvasive detection of specific biomarkers for particular traits underlying the pathological process (Clark et al. 2008). Given the complexity and sometimes overlapping characteristics of these disorders and despite recent advances in molecular neurosciences, it is unlikely that a single biomarker will be able to provide the diagnostic certainty required for the early detection of neurodegenerative diseases like AD, especially for the identification of at-risk individuals before the development of the typical phenotype. Therefore, a multimodality approach combining biochemical and neuroimaging methods is warranted (Shaw et al. 2007).

Biomarkers are important as they can be used to identify the risk of developing a disease (antecedent biomarkers), aid in identifying disease (diagnostic biomarkers), assess disease evolution (progression biomarkers), predict future disease course (prognostic biomarkers) or evaluate and/or customise therapy (theranostic biomarkers). While CSF A $\beta$  and tau, structural and molecular neuroimaging (both FDG and A $\beta$  imaging) are all good—especially if combined—diagnostic biomarkers for AD, evaluation of the data available to date suggests that A $\beta$  imaging and CSF assessments of A $\beta$  are good antecedent biomarkers at the preclinical and prodromal stages of the disease (Jack et al. 2010; Ossenkoppele et al. 2011; Villemagne et al. 2011b). Conversely, CSF assessments of tau and p-tau, structural neuroimaging and FDG seem to be excellent biomarkers of disease progression (Jack et al. 2010). Despite the fact that A $\beta$  accumulation is still ongoing at the AD stage (Villemagne et al. 2011b; Villain et al. 2012) and in contrast to what is observed at the preclinical and prodromal phases (Pike et al. 2007; Villemagne et al. 2008a; Cohen et al. 2012), A $\beta$  burden at this stage is not correlated with markers of

neurodegeneration, disease severity or cognitive impairment (Hyman 2011; Karran et al. 2011). A review of the literature shows that quantification of  $A\beta_{1-42}$ , total tau and p-tau in CSF, FDG and a long list of assessments of global or regional brain atrophy as well as white matter hyperintensities with MRI have all been proposed as predictors of conversion to AD (Chang and Silverman 2004; Smith et al. 2008; Jack et al. 2010). While larger longitudinal studies will further clarify the role of  $A\beta$  imaging in predicting conversion from MCI to AD, one of the most important conclusions to be drawn from these studies is that the likelihood of developing AD in a cognitively unimpaired individual with a low  $A\beta$  burden scan is extremely small (Villemagne et al. 2011b).

Another aspect to be considered is prediction of therapeutic response. As new therapies enter clinical trials, the role of  $A\beta$  imaging in vivo is becoming increasingly crucial.  $A\beta$  imaging allows the in vivo assessment of brain  $A\beta$  pathology and its changes over time, providing highly accurate, reliable and reproducible quantitative statements of regional or global  $A\beta$  burden in the brain. As mentioned before, therapies, especially those targeting irreversible neurodegenerative processes, have a better chance to succeed if applied early, making early detection of the underlying pathological process so important. Therefore,  $A\beta$  imaging is an ideal tool for the selection of adequate candidates for anti- $A\beta$  therapeutic trials while also monitoring—and potentially predicting—treatment response, thus aiding in reducing sample size, minimising cost while maximising outcomes. Preliminary studies are already showing the utility of this technique (Rinne et al. 2010; Ostrowitzki et al. 2012). These preliminary results, taken together with the results from longitudinal studies, support the growing consensus that anti- $A\beta$  therapy to be effective may need to be given early in the course of the disease, perhaps even before symptoms appear (Sperling et al. 2011b), and that downstream mechanisms may also need to be addressed to successfully prevent the development of AD. Furthermore, the slow rate of  $A\beta$  deposition indicates that the time window for altering  $A\beta$  accumulation prior to the full manifestation of the clinical phenotype may be very wide (Villemagne et al. 2011b).

The introduction of radiotracers for the noninvasive in vivo quantification of  $A\beta$  burden in the brain has revolutionised the approach to the evaluation of AD.  $A\beta$  imaging has extended our insight into  $A\beta$  deposition in the brain, where  $A\beta$  burden as measured by PET matches histopathological reports of  $A\beta$  distribution in aging and dementia, and it appears more accurate than FDG for the diagnosis of AD and is an excellent aid in the differential diagnosis of AD from FTLD (Mathis et al. 2005, 2007; Johnson 2006; Villemagne et al. 2008a, 2012b; Jagust 2009; Rabinovici and Jagust 2009; Drzezga 2010; Klunk 2011). ApoE  $\epsilon 4$  carriers, independent of diagnosis or disease severity, present with higher  $A\beta$  burden than non- $\epsilon 4$  carriers, and high retention of  $A\beta$  radiotracers closely corresponds with low CSF  $A\beta$  levels and increasing age (Reiman et al. 2009a; Fagan and Holtzman 2010; Morris et al. 2010; Rowe et al. 2010). Although  $A\beta$  burden as assessed by PET does not strongly correlate with cognitive impairment in AD, it does correlate with memory impairment and a higher risk for cognitive decline in the aging population and MCI subjects. This correlation with memory impairment, one of the earliest symptoms of AD, suggests that  $A\beta$

deposition is not part of normal aging, supporting the hypothesis that A $\beta$  deposition occurs well before the onset of symptoms and it likely represents preclinical AD in asymptomatic individuals and prodromal AD in MCI. Further longitudinal observations, coupled with different disease-specific biomarkers to assess potential downstream effects of A $\beta$ , are required to confirm this hypothesis and further elucidate the role of A $\beta$  deposition in the course of Alzheimer's disease.

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