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Abstract

Recent developments of PET amyloid ligands have made it possible to visualize the presence of Aβ deposition in the brain of living participants and to assess the consequences especially in individuals with no objective sign of cognitive deficits. The present review will focus on amyloid imaging in cognitively normal elderly, asymptomatic at-risk populations, and individuals with subjective cognitive decline. It will cover the prevalence of amyloid-positive cases amongst cognitively normal elderly, the influence of risk factors for AD, the relationships to cognition, atrophy and prognosis, longitudinal amyloid imaging and ethical aspects related to amyloid imaging in cognitively normal individuals. Almost ten years of research have led to a few consensual and relatively consistent findings: some cognitively normal elderly have Aβ deposition in their brain, the prevalence of amyloid-positive cases increases in at-risk populations, the prognosis for these individuals is worse than for those with no Aβ deposition, and significant increase in Aβ deposition over time is detectable in cognitively normal elderly. More inconsistent findings are still under debate; these include the relationship between Aβ deposition and cognition and brain volume, the sequence and cause-to-effect relations between the different AD biomarkers, and the individual outcome associated with an amyloid positive versus negative scan. Preclinical amyloid imaging also raises important ethical issues. While amyloid imaging is definitely useful to understand the role of Aβ in early stages, to define at-risk populations for research or for clinical trial, and to assess the effects of anti-amyloid treatments, we are not ready yet to translate research results into clinical practice and policy. More researches are needed to determine which information to disclose from an individual amyloid imaging scan, the way of disclosing such information and the impact on individuals and on society.

1. Introduction

This review will focus on amyloid imaging in cognitively normal elderly, asymptomatic at-risk populations, and individuals with subjective cognitive decline. It is one of two side-to-side review papers, the second one by Vandenberghe et al. [1] (this issue) focusing on amyloid imaging in cognitively impaired populations. The present effort extends from a talk presented at the Alzheimer's Association International Conference (http://www.alz.org/aaic/overview.asp) in July 2012 on amyloid imaging in preclinical individuals. It will cover the prevalence of amyloid-positive cases amongst cognitively normal elderly, the influence of risk factors for AD, the relationships to cognition, atrophy and prognosis, longitudinal amyloid imaging and ethical aspects related to amyloid imaging in cognitively normal individuals. The goal was not to be exhaustive but to give weighted opinions on most challenging contemporary debates based on our current state of knowledge. Thus, some topics will not be covered, such as the relationships with other brain imaging modalities (e.g. FDG-PET, task-related and resting-state functional MRI, diffusion tensor imaging) and CSF biomarkers, or discussion on the similarities and differences between the various PET amyloid ligands.

β-amyloid (Aβ) deposition is one of the main hallmarks of Alzheimer's disease and is thought to play a central role in the neurodegenerative process characterizing this disease [2,3]. Neuropathological studies have shown more than 20 years ago that substantial level of Aβ deposition can be found in the autopsied brain of cases with documented normal cognition . Recently, PET amyloid ligands have been developed, the first one (except from FDDNP see below) being the ^{11}C-Pittsburgh Compound B (^{11}C-PIB) PET ligand [8], followed by the recently Food and Drug Administration (FDA) -approved ^{18}F-florbetapir [9,10] and other 18F-labelled ligands [11]. Thanks to these developments, we entered a new exciting area where it is possible to visualize plaques in the brain of living participants. This offers the unique opportunity to get further - including longitudinal - information in these individuals, so as to improve our understanding of the consequence of the presence of Aβ deposition in the brain of cognitively normal elderly, and more generally of the role of Aβ deposition in early AD pathological processes. Note that studies will be reviewed in what follows irrespective of the PET amyloid ligand being used, with the exception of studies using FDDNP (e.g. [12]) that will not be included here as we

aimed at specifically addressing issues related to Aβ while FDDNP binds to both Aβ and tau abnormalities.

2. The presence of Aβ in the brain of cognitively normal elderly and at-risk populations

2.1. The prevalence of amyloid-positive cases within cognitively normal elderly

Consistent with neuropathological studies [7], neuroimaging amyloid-PET studies found amyloid-positive cases within cognitively normal ("healthy") older people. The first in-vivo ^{11}C-PIB PET study reported one ^{11}C-PIB-positive case amongst the control elderly [8], and this has been consistently reported since then. A bimodal distribution of neocortical ^{11}C-PIB values is usually reported within elderly subjects with normal cognition (e.g. [13]), though there is recent and accumulating evidence for intermediate cases (see below). A majority of healthy elderly shows low ^{11}C-PIB retention, but part of them shows distinctly elevated ^{11}C-PIB retention in regions that ultimately develop heavy Aβ loads in AD patients, especially the posterior cingulate cortex – precuneus and the anterior cingulate cortex – medial orbitofronal cortex [7,14–24]. While neuropathological and amyloid-PET neuroimaging studies have thus consistently demonstrated that some elderly with normal cognition may have Aβ deposition in their brain, what is less consensual is the prevalence of cognitively normal elderly with an amyloid-positive scan. Extremely variable proportions have been reported in the literacy ranging from 0% [25] to 47% [26], with prevalence of 10 to 30% being more frequently reported [27] (see **Table 1** for examples). Several factors are likely to explain this considerable variability. This could reflect methodological differences across studies (e.g. the amyloid ligand or the method used to define a positivity threshold), or genuine differences due to the samples and reflecting differences in the screening process or in genetic, social, ethnical and environmental factors (see "The influence of at-risk factors" below).

Actually, the particular PET amyloid ligand that is used is probably not the main element to account for this large variability, as several studies reported a very good correlation between the different PET amyloid ligands [28–30] (see also the side article by Vandenberghe et al. [1] in this issue, for further details). By contrast, the method used to define positivity probably accounts for a significant part of

this variability. They are clearly negative and clearly positive cases but there are also intermediate cases (**Figure 1**). As further discussed below, these intermediate cases represent a non-negligible proportion of the cognitively normal elderly and their classification as positive or negative is highly sensitive to the method, which will thus significantly impact on the proportion of amyloid-positive scans. Note that not much is known about these intermediate cases, and this would be an important topic for future research. One previous work showed that intermediate cortical PIB values seem to reflect both lower number of elevated PIB regions and lower PIB value in these regions, through in the same network, as compared to the clearly positive cases [31]. However, further studies are needed, notably longitudinal studies to follow the progression of amyloid deposition in these intermediate individuals as well as to assess their risk of conversion as compared to the positive and negative categories.

There are many methodological factors that may influence the classification of cases (see [32] for example): the method used to read the scan (either through visual inspection or using quantitative values), the regions that are considered, the values that are used, e.g. corrected from partial volume effects or not, scaled using the pons or the cerebellum or another region, etc. It has been proposed for example that the pons may be more suitable as a reference region in specific cases, e.g for longitudinal studies [33] or when amyloid deposition may be present in the cerebellum (e.g., in early-onset familial AD) [34,35]. Another determining factor is the method used to define the threshold from which a scan is classified as positive or negative. Numerous methods have been used in the literature: clustering analyses, the 95th percentile, the iterative outlier approach, an absolute cut-off (e.g. SUVR > 1.50), the mean + 2SD of healthy elderly controls, the mean + 2SD of healthy young controls (supposedly devoid of $A\beta$ deposition), for an non-exhaustive list. The study by Mormino et al. [31] is a good illustration of this point, as it showed that when using two different methods to define the threshold (i.e. the iterative outlier approach versus the mean + 2SD of young healthy controls), the percentage of ^{11}C-PIB-positive individuals amongst healthy elderly varied considerably (from 15 to 35%) (see also [18]). In the IMAP project conducted in the Inserm U1077 Unit in Caen (France), 3 out of 36 (8%) cognitively normal elderly were clearly positive (i.e. showed $A\beta$ load in the range of AD patients).

Only these 3 cases were classified as amyloid-positive using the iterative outlier approach, while 9 additional cases were classified positively when using a group of 12 participants younger than 55 yrs (under the assumption that these individuals have no Aβ deposition and therefore the corresponding PET signal should only reflect noise; **Figure 1**). As a whole, intermediate cases can be as frequent as 20-25% in cognitively normal elderly populations and they may be responsible for a large part of the variability in the percentage of amyloid-positive cases. This is however not the only reason for differences in the proportion of amyloid-positive elderly: the screening procedure and selection criteria used in the different studies probably also accounts for a large part of this variability. Several factors are known to influence the proportion of amyloid-positive cases as discussed in the following section, and these factors may be more or less represented or controlled for according to the studies.

2.2. The effects of age and ApoE4

The two main risk factors for AD, namely age and ApoE4, have been consistently shown to have a significant impact on Aβ deposition in normal elderly [36]. For example, the prevalence of amyloid-positive cases within healthy older participants raised from 18% in the seventh decade to 60% in those over 80 yrs [37] or from 0% at ages 45-49 yrs to 30% in the eighth decade in another study [24]. Note that a linear relationship was found between Aβ deposition and age even within the ^{11}C-PIB-negative cases when assessing a wide age range (23-80 years) [28]. Similarly, amongst cognitively normal elderly, 49% of ApoE4 carriers were ^{11}C-PIB-positive while they were only 21% within the non-carriers [37]. This effect is reported in many studies and is found to be dose-dependent and region-specific, i.e. to be more pronounced in some brain regions (such as temporo-parietal areas) than in others [24,38–41]. Age and ApoE are likely to account for part of the variability in the proportion of amyloid-positive cases as there are great differences between some studies/samples (e.g. 43% ApoE4 in [37] versus 22% in [42], and a mean age of 69.8 years old in [37] versus 78 years old in [26]).

2.3. Individuals with subjective cognitive decline

Individuals with subjective cognitive decline are elderly who present with a cognitive complaint but do not show any significant cognitive deficit compared to subjects their age. This is a rather broad definition that may refer to many different entities as consensual criteria for subjective cognitive decline are missing to date. The presence or not of individuals with subjective cognitive decline is another factor that may influence the proportion of amyloid-positive cases in elderly cohorts as this criteria is not always controlled for. Thus, Perrotin et al. [43] showed increased proportion of ^{11}C-PIB positive cases amongst elderly who consider that their memory is the same or worse relative to people their age, compared to those who think their memory is better. A relationship between a subjective memory complaints composite score and cortical PiB binding has also been reported [44], but other reports found no significant difference in global neocortical ^{11}C-PIB between healthy elderly with and without subjective cognitive decline [45]. The significance of the effect thus likely depends on the cohort and the method to determine amyloid-positivity (see above) as well as to assess subjective cognitive decline. The different risk-factors may also interact, as suggested for example by the finding that subjective cognitive decline was only associated with elevated ^{11}C-PIB binding in ApoE4 carriers [37].

2.4. The effects of other genetic and environmental factors

A familial, and especially maternal, history of AD has also been reported to be associated with increased ^{11}C-PIB SUVR [46]. This effect was shown to be independent from that of ApoE4 [47], suggesting that non-APOE susceptibility genes for AD influence AD biomarkers. In the same line, a very interesting study by Scheinin et al. [48] assessing cognitively preserved monozygotic and dizygotic cotwins of persons with AD showed that cognitively normal dizygotic cotwins had normal low ^{11}C-PIB SUVR, while the monozygotic cognitively normal cotwins had abnormally elevated SUVR, almost at the level of their AD cotwins. This suggests that genetic factors at least partly determine the development of Aβ plaques, but also that there may be environmental/acquired factors that modulate the relationship between brain amyloidosis and cognition. This view agrees with studies

highlighting the effect of education [49], lifetime cognitive engagement [50], and physical exercise [51,52] on ^{11}C-PIB deposition or on its association to cognition or neuronal injury. In the same line, ApoE4 carriers who engaged in moderate levels of exercise had a lower amyloid burden than ApoE4 carriers with lower levels of exercise and this effect of exercise was not seen in the noncarriers [52]. While the effects of these different factors are not clear-cut, with some discrepancies between studies, they overall indicate that, consistent with the reserve theory [53], higher reserve proxies are associated with reduced amyloidosis or Aβ-related cognitive or neuronal deficits.

2.5. Asymptomatic mutation carriers for the early-onset familial form of AD

Finally, further insights in this question arise from studies on the early onset familial form of AD (EOFAD). Thus, studies conducted in carriers of mutations that lead to EOFAD showed that increased amyloid load can be detected at a presymptomatic stage [54–56]. Interestingly, the topographical pattern is slightly different from that observed in sporadic AD (**Figure 2**), with a predominance of Aβ deposition in the striatum of asymptomatic EOFAD while the neocortex is less systematically and less significantly involved than in sporadic AD, independently of mutation type [54–56] (see [57,58] for reviews). Increased ^{11}C-PIB binding has also been reported in the thalamus and the cerebellum in asymptomatic EOFAD [55,56].

As for the timing and sequence of the apparition of brain Aβ deposition, a recent publication in EOFAD showed that Aβ deposition can be detected 15 years before expected symptom onset - corresponding to the parental age at onset as determined by a semistructured interview in which family members were asked about the age of first progressive cognitive decline [59]. This was also true for increased CSF tau and brain atrophy, while changes in CSF Aβ-42 were detected 25 years before, and hypometabolism and memory deficits 10 years before expected symptom onset. This is a very informative study from the DIAN collaborative study gathering the largest MRI and PET multicentre database on this population. These findings were confirmed and extended in two other studies from a large Columbian kindred suggesting that neurodegenerative changes could precede or at least

accompany evidence of Aβ deposition [34,60]. These results are crucial as they question the prevailing amyloid hypothesis and current models of the dynamic and sequence of the different biomarkers [61–65] that predict that Aβ deposition occurs first and is responsible for neurodegeneration. However, generalization to the common sporadic form of AD from results obtained in familial AD should be considered with caution. Results from comparable studies in preclinical sporadic AD (such as the ADNI or AIBL cohorts) and others, are still warranted to determine the sequence and timing of biomarkers in sporadic AD (see also below).

Altogether, many genetic risk factors involved in familial or sporadic AD were found to influence Aβ deposition, suggesting that Aβ load is highly heritable [58]. However, healthy life and stimulating environment seems to allow delaying/reducing Aβ deposition in the brain and/or its effect on brain integrity and cognition.

3. Relation to clinical status, cognitive performances and brain volume

3.1. Relation to concomitant cognition and brain volume

There have been quite numerous studies assessing the relation to cognition, even specifically within normal elderly, but the results remain overall puzzling: there are almost as many studies showing no significant relationships [18,20,66–71] as those showing a significant effect, and in the latter the relationship was rarely strong and general but rather modest and/or concerned a specific population with diverging results according to studies [40,66,72–77]. For example, relationships are usually reported with episodic memory deficits, but a study also reported a link with processing speed and working but not episodic memory [77]. Moreover, discrepant results have been reported in a same study with two CNE samples from two different databases [66], and significant relationships have been observed only within females [78], non ApoE4 carriers [78], or mainly in ApoE4 carriers [40] or low educated cognitively normal elderly [49]. In another study from the AIBL cohort, the relationships with episodic memory was found to concern only inferior temporal Aβ deposition [73], or only normal elderly with subjective cognitive decline [45]. Note that in the same cohort from the AIBL study, cognitively normal elderly without subjective cognitive decline showed a reverse relationship with higher memory performances in ^{11}C-PIB-positive compared to ^{11}C-PIB-negative cases [79]. Similar findings have been reported in a previous preliminary study [18]. These ^{11}C-PIB-positive "super-performers" also had larger temporal lobe, which suggests that they represent a particularly resistant subsample with larger brain reserve [79] (see also above for the effect of education and brain reserve). By contrast, in normal elderly with subjective memory decline, a relation was observed in the more expected direction with increased atrophy as amyloid load increases [45]. In this study, the relationship was assessed voxel-to-voxel and local correlations were found in individuals with subjective cognitive decline within the posterior cingulate cortex and medial frontal area, which are the regions of highest Aβ deposition. There was no relationship within the hippocampus where atrophy predominates in AD, suggesting that atrophy is not due to local Aβ in this structure but involves other neuropathological processes. Distant (temporal) Aβ deposition for example has been found to be related to hippocampal atrophy [22], and additional, partly independent, processes are thought to be involved [73,80].

Neurofibrillary tangles are very likely to be implicated as these lesions develop very early in the hippocampus and they are known to correlate to neuronal loss and atrophy. When assessed in healthy elderly independently from whether or not they have subjective cognitive decline, findings were discrepant. Significant hippocampal atrophy has been reported in amyloid-positive cases in some studies [20,81], but not in others [21,22], and temporal pole [21] or anterior and posterior cingulate cortex [20,82] and prefrontal and lateral parietal cortex [82] atrophy or thickness reduction have been reported as well. When assessed linearly, a significant correlation has been found between global ^{11}C-PIB and hippocampal atrophy in normal elderly [37,66], thought negative findings have been reported as well [82]. Finally, a recent study report a covariation between increase global ^{11}C-PIB and decrease grey matter volume including in the medial and lateral temporal lobe, and medial frontal and posterior cingulate cortex [75].

As a whole, the relationships between cerebral Aβ deposits and concomitant cognitive performances or gray matter volume/thickness are complex and subtle. This probably reflects the fact that, if Aβ deposition has a role in neurodegeneration and cognitive deficits, it is probably indirect and/or blurred by the time decay between the different biomarkers [63], and/or by the intervention of other probably partly independent factors (e.g. tau-related changes, decreased metabolism, white matter abnormalities and disconnection, cognitive and brain compensation, etc.). There are accumulating evidences that Alzheimer's disease is a multifactorial disease with different and partly independent subtending processes rather than a single-process-driven pathology [68,80,83]; see http://**www.alzforum**.org/res/for/journal/detail.asp?liveID=199 for a live discussion on this topic).

3.2. Relation to prognosis - later changes in clinical status, cognition or brain volume

Longitudinal studies assessing the relationships between baseline Aβ deposition and subsequent changes in cognition or brain volume usually report that the presence of Aβ deposition in the brain of cognitively normal elderly is associated with a worse prognosis. Thus, Villemagne et al. [39] showed that 5 out of 32 (16%) of the ^{11}C-PIB-positive cognitively normal elderly developed MCI or AD by 20

months and 8 out of 32 (25%) by 3 years while only one out of 73 ^{11}C-PIB-negative normal elderly developed MCI. Also, elevated Aβ deposition in cognitively normal elderly was shown to be related to greater clinical worsening (based on the CDR and/or ADAS-Cog scales) [42,84] and cognitive decline (in episodic and working memory and visuospatial ability) [20,69]. In Doraiswamy et al. [42], 23.5% of CDR0 amyloid-positive cognitively normal elderly converted to CDR0.5 within 18 months versus 5.5% within the amyloid-negative elderly. Finally, one longitudinal MRI study showed that ^{11}C-PIB-positive cognitively normal elderly exhibited faster gray matter atrophy compared to ^{11}C-PIB-negative cases at a group level [85]. Moreover, the amount of neocortical Aβ deposition correlated with the rate of subsequent atrophy in AD-sensitive brain areas (i.e. the temporal neocortex, hippocampus, posterior cingulate cortex, and angular gyrus), which was itself related to the rate of subsequent cognitive decline. These findings are consistent with a preliminary report in 13 healthy controls by Scheinin et al. [86] or with findings in patients with MCI [87] (see the side article by Vandenberghe et al. [1], this issue), as well as with studies showing that low CSF Aβ was associated with a faster rate of atrophy in similar AD-sensitive brain areas [88–91]. It should be noted however that the findings in cognitively normal elderly should be considered carefully, keeping in mind that they were mostly obtained in community-recruited cohort studies where selection biases may be present, which may have an influence not only on the rate of amyloid-positive cases as discussed above, but also on the rate of conversion to AD and on the interaction between both factors (i.e. on the rate of conversion to AD of the amyloid-positive elderly). Consistent with this statement, the rate of conversion to AD in amyloid PET studies is usually particularly elevated, more than what would be expected given the incidence reported in the general population (see e.g. [92]). Although this questions the absolute number of converters within the amyloid-positives, these findings as a whole indicate that, on average, the prognosis in a group of individuals having Aβ in the brain, even if they are asymptomatic, is worse than that of a group of individuals with no Aβ.

4. The new research criteria for preclinical AD

The considerable advances in neuroimaging and cerebrospinal biomarkers for AD in the last two decades, with amyloid imaging being the most recent and certainly the most notable of these developments, led to the revision of the NINCDS-ADRDA clinical diagnosis criteria for AD [93]. Several propositions have been published by different groups and addressing different clinical populations [94–98], and the present review will focus on the recommendation for the preclinical stages of AD [98]. These new criteria also take into account the hypothetical model of the chronology of the different biomarkers [63] itself largely based on the amyloid cascade hypothesis [2], and consistently propose three stages in the preclinical phase: $A\beta$ is present in the first stage without neuronal injury (stage 1), then neuronal injury is detected as well (stage 2), and then subtle cognitive decline appears (stage 3). When assessed in a population-based sample of 450 CNE, 43% of individuals were negative for the 3 biomarkers so they were considered as stage 0, and 16% were in stage 1, 12% in stage 2 and 3% in stage 3 [99]. In addition, another category had to be added to account for the whole population, as 23% of subjects didn't fit into any group because they had AD-type neuronal injury (i.e. hippocampal atrophy and/or hypometabolism in the angular gyrus, posterior cingulate and inferior temporal cortex) without evidence of $A\beta$ deposition. As this doesn't fit with the biomarkers chronology model that predicts that $A\beta$ appears before neurodegeneration, these individuals are suspected to have non-AD pathology and were called as SNAP (for Suspected Non-Alzheimer's disease Pathophysiology). Longitudinal studies with a clinical follow-up of individuals in the different stages/categories are extremely important in the current context to confirm this view but also more generally to validate the diagnosis criteria and current dynamic biomarkers models and further our understanding of the mechanisms underlying the disease. Actually, a recent publication provides first insights to these questions by showing the clinical outcome of participants according to each stage [100]. This study showed that the more positive biomarkers you have the more likely you are to convert, which confirms the usefulness of these biomarkers. It didn't allow to validate the chronology of biomarkers proposed by the model however, as the rate of conversion to MCI or dementia was similar in individuals in stage 1, i.e. who only had $A\beta$ deposition in their brain (11%) as compared to the SNAP subjects, i.e. those having only neuronal injury but no $A\beta$ (10%). This 10

percent conversion rate within the SNAP group was thus striking, but could still reflect the fact that they have non-AD related pathologies such as cerebrovascular disease. A recent publication however reveals that these so-called SNAP cases were indistinguishable from preclinical AD stages 1-3 on a variety of measures including those associated with the most frequent non-AD pathophysiological processes, i.e. cerebrovascular disease and α-synucleinopathy [101]. The authors concluded that the initial appearance of brain injury biomarkers in cognitively normal elderly individuals may not depend on β‑amyloidosis, which thus contradicts both the chronology proposed in the currently prevailing model and the amyloid cascade hypothesis. This, together with other arguments (e.g. [102–104],) will probably further motivate researchers to consider alternatives to the amyloid hypothesis where Aβ promotes but is not necessarily responsible for, AD-related neurodegeneration [104].

5. Longitudinal amyloid imaging

As a whole, except in the first studies where sample sizes were relatively small and changes were not statistically significant [26,86], longitudinal amyloid imaging studies showed significant increase in Aβ load in cognitively normal elderly of about 1% per year [33,39,105–107]. This increase was found to be higher in amyloid-positive than in negative cognitively normal elderly, and lower in cognitively normal elderly compared to MCI or AD though this was due to the fact that there were more amyloid-negative cases within the cognitively normal elderly than within the MCI or AD patients; when controlling for the ^{11}C-PIB status, no difference was found in the rate of ^{11}C-PIB accumulation between clinical groups [33]. Most significant changes were observed in prefrontal, parietal, lateral temporal and occipital cortex [33,106] and anterior and posterior cingulate cortex [106]. Increase in ^{11}C-PIB over time in amyloid-negative cognitively normal elderly was found to be lower than in amyloid-positive but still significant. Individual analyses showed that there were more ^{11}C-PIB accumulators (i.e. individuals showing significant ^{11}C-PIB accumulation / increase over time) amongst ^{11}C-PIB-positive (50%) than amongst ^{11}C-PIB-negative (29%) cognitively normal elderly [33]. The incidence of conversion from negative to positive within cognitively normal elderly was about 3% per year, and raised 7% in the ApoE4 carriers [107]. The rate of ^{11}C-PIB accumulation remains higher in

the ^{11}C-PIB-positive cases when only considering the accumulators, suggesting that those with higher ^{11}C-PIB have greater rate of ^{11}C-PIB accumulation, while this trend tends to reverse in those with high baseline ^{11}C-PIB retention, consistent with the concept of a saturable process of Aβ deposition as the ^{11}C-PIB retention reaches highest values [33]. Further discussion on the dynamic of Aβ all over the course of the disease including in clinical stages will be provided in the side review by Vandenberghe et al. [1] (this issue).

6. Ethical considerations

The progressive discovery of biomarkers for AD that peaks with amyloid neuroimaging, their use in the new proposed criteria for AD including specifically for preclinical AD, the recent approval of Amyvid (florbetapir F18 injection) by the FDA on April 9th 2012, altogether revive the debate on ethical challenges of preclinical AD that has been already, at least partly, addressed with the development of ApoE genotyping and predictive genetic testing. There have been an increasing interest in this question recently, and several groups develop specific studies and publish reviews fully-dedicated to this issue [108–113]. The present review was not aimed at providing a detailed overview on ethical and social issues associated with preclinical AD. However, inspired by these authors, the main questions will be highlighted as they are crucial when dealing with amyloid imaging in preclinical populations.

Thus, early diagnosis in general, amyloid imaging in preclinical population in particular, raise important ethical issues as regard to disclosure of these information to individuals. There is a distinction between clinical assessments versus research. Researchers have no obligation to disclose biomarker results to participants, and the informed consent explains to them why they will not be given such information [112]. As for the clinic, we are far from a routine use in clinical practice for the preclinical diagnosis for AD: amyloid imaging doesn't fulfill the requirements for a screening test (in terms of cost, accuracy, availability, etc) according to the principles and practice of screening for disease published by the World Health Organization [114]. FDA approval is only for cognitively impaired patients, and the use of biomarkers in preclinical AD is only for research. However, scientists

and clinicians should prepare to face the problem, notably to anticipate the hopeful future development of disease-modifying treatments.

While it is quite clear that there are amyloid-positive cases amongst cognitively normal elderly, and that their risk of conversion to AD is probably higher than for amyloid-negative cognitively normal elderly, it is also clear that not all amyloid-positive cognitively normal elderly will convert to AD at least in the following couple of years. Thus, the rate of conversion to MCI/AD in amyloid-positive cognitively normal elderly is about 15-25% within the following 2-3 years (see above), which means that about 80% will remain stable over this period. The AIBL study offers one of the largest database with amyloid PET imaging and with the longest follow-up time, and it shows that some ^{11}C-PIB-positive cognitively normal elderly remain cognitively stable even after 6 year follow-up (Rowe and Villemagne, personal communication). This leads to the first following question: is it ethical to deliver an amyloid-scan result while not all amyloid-positive individuals will develop AD. This means that what is delivered is not diagnosis but risk information. This distinction is very important as it should be perfectly clear, for the clinician of course but also for the patient and his family, that what is disclosed from an amyloid scan is information about the presence of $A\beta$ deposition in the brain, associated with a risk to develop AD, but not on the diagnosis of AD itself. This is thus the same situation as for disclosing ApoE genotype and scientists thus take their inspiration from the relatively abundant literacy on disclosing genetic information. This leads to a second question that more generally applies to early AD diagnosis: is it ethical to deliver the risk information related to an amyloid-scan result while there is no treatment? The growing distance between scientific advances in terms of diagnosis versus treatment and the uncoupling between the diagnosis and the clinical expression of the disease also raise ethical issues. When trying to answer to these questions, one should also take into account patient's right to know and find the balance between the patient's desire to know his risk developing AD and the clinician's desire to mitigate the potential harm of that information. These are very difficult questions to answer, as of course there are both advantages and disadvantages in disclosing risk information such as the results of an amyloid scan in asymptomatic

individuals and in preclinical AD diagnosis (see **Table 2** for examples of advantages and disadvantages).

Our advances in terms of preclinical diagnosis and biomarkers should thus be paralleled by evidence-based advances in our knowledge on the way to disclose this information and on its psychological implications, as well as by societal and legislative evolution. More specifically, studies are needed (and are currently under progress) to track the emotional and physical impact of the disclosure, and to develop and disseminate best practice guide on how to disclose the result of an amyloid scan. Again, such procedures have already been defined for disclosure of genetic information (such as providing time for reflection prior to disclosing results, psychological support, delivery in a face-to-face meeting, etc) that provide a significant basis for adaptation to the case of amyloid imaging in preclinical populations.

We cannot work on amyloid imaging in preclinical AD without anticipating the related ethical challenges. Clearly, we are not ready yet for the diagnosis of preclinical AD. There are numerous challenges that should first be faced, several essential questions of ethical implications that still need to be answered; our knowledge on how patients actually react to early diagnosis is still too scarce and preliminary steps are thus needed to translate research results into clinical practice and policy.

7. Conclusion

As a whole, there are evidences for which there is absolutely no doubt on: some cognitively normal elderly have Aβ deposition in their brain, the prevalence of amyloid-positive cases increases in at-risk populations, the prognosis for these individuals (as a group) is worse than for those with no Aβ deposition, and significant increase in Aβ deposition over time is detectable in cognitively normal elderly. Other points are more obscure: the relation between Aβ deposition and AD-related changes (cognition, atrophy, hypometabolism and connectivity) is complex, the sequence and cause-to-effect relationships between the different biomarkers is challenged, and the individual outcome associated with an amyloid-positive scan is still unknown: will all amyloid-positive elderly eventually develop

AD and when? Further studies are needed to know how to translate group findings into individual use, i.e. how to use amyloid imaging to support AD diagnosis in preclinical individuals. Preclinical amyloid imaging also raises important ethical issues. There is a distinction between clinic and research for the use of amyloid imaging, and between clinicians and researchers for the disclosure of information. Amyloid imaging is definitively useful to understand the role of Aβ in early stages, to define at-risk populations for research or for clinical trial, and to assess the effects of anti-amyloid treatments. However, we are not ready yet to translate research results into clinical practice and policy. The considerable advances of research in terms of amyloid imaging, biomarkers and preclinical diagnosis over the last decade should be paralleled by significant progress in our knowledge on the way of disclosing such information and its impact, as well as societal and legislation adaptation to anticipate the future where preclinical diagnosis and disease-modifying treatment will hopefully be available.

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Table 1: Examples of the prevalence of amyloid-positive cases by clinical group. This illustrates the variability in the percentage of amyloid-positive cases amongst cognitively normal elderly (CNE) according to studies, probably due to variability in the methods and in the samples (see text for details). The prevalence in patients with mild cognitive elderly (MCI) and patients with Alzheimer's disease (AD) is also provided for the sake of comparison (although the present review only focuses on cognitively normal elderly).

References	Amyloid ligand	CNE		MCI		AD	
		n	% Aβ +	n	% Aβ +	n	% Aβ +
[37]	PIB	177	33%	57	68%	53	98%
[26]	PIB	19	47%	65	72%	19	89%
[31]*	PIB	75	15-35%	-	-	10	90%
[25]	PIB	26	0%	31	55%	-	-
[115]	PIB	20	30%	23	40%	13	100%
[19]	PIB	20	30%	17	53%	8	100%
[116]	PIB	13	15%	29	72%	-	-
[15]*	PIB	20	10-20%	-	-	10	90%
[117]*	Florbetapir	82	21-28%	60	40-47%	68	81-85%
[77]	Florbetapir	87	20%	-	-	-	-
[118]*	Florbetapir	78	14-23%	-	-	-	-
[42]	Florbetapir	69	14%	51	37%	31	68%
[39]	Florbetaben	32	16%	20	60%	30	97%
[28]	Flutemetamol	15	7%	20	50%	27	93%

* Studies that used different methods to define the threshold for amyloid-positivity, thus leading to different proportions of amyloid-positive cases; % Aβ +: percentage of amyloid-positive cases within the clinical group.

Table 2: Advantages and disadvantages of disclosing the result of an amyloid-scan to cognitively normal elderly.

Advantages	Disadvantages
A correct diagnosis may be clarifying and appreciated by the patient and his/her relatives	The result of AD biomarker testing is potentially harmful, especially absent an effective disease-modifying treatment for AD (>55 yrs fear AD more than any other disease including cancer)
Opportunity to reduce suffering and costs for both patients and society	Problems related to inconclusive scans (uncertainty, reproducibility and accuracy)
Enables early decision making when patients still have full decision competence + help in receiving assistance to cope with progressive decline + from health care system	Risks of stigmatization, feeling of hopelessness, agony and despair, anxiety, depression, increase of suicide attempts and euthanasia request [109]
Possibility to take even unproven intervention in an effort to reduce the risk: a positive scan might encourage lifestyle changes (diet, exercise, cognitive training, etc.) even if effects are modest at best	Risks of affecting insurance premiums, right to drive, work conditions
Relief related to a negative amyloid imaging scan	Ethical consequences of false diagnosis could be serious

Figure 1: Illustration of positive, negative, and intermediate cases within the cognitively normal elderly. These data are issued from the IMAP study (Inserm U1077, Caen, France). Each circle represents the mean neocortical ^{18}F-florbetapir SUVR from an individual. The majority (67%) of healthy controls older than 60 years (HC > 60 yrs) is clearly negative (i.e. their SUVR value is within 2SD of the controls younger than 60 years = HC < 60 yrs). Three cases were clearly positive (i.e. classified as positive both compared to younger controls and using the iterative outlier approach). There were 25% of intermediate cases, i.e. cases classified as positive or negative according to the method.

Figure 2: Illustration of the brain distribution of ^{18}F-florbetapir in six cases from the IMAP project (Inserm U1077, Caen, France). The figure shows disproportionate binding of ^{18}F-florbetapir in the caudate nucleus in the asymptomatic and symptomatic mutation carriers for the early-onset familial form of AD compared to both sporadic AD cases and amyloid-positive cognitively normal erlderly.