Aß Imaging: Feasible, Pertinent, and Vital to Progress in Alzheimer's Disease

Eur J Nucl Med Mol Imaging (2012) 39:209–219
DOI 10.1007/s00259-011-2045-0

EDITORIAL

Aβ Imaging: feasible, pertinent, and vital to progress in Alzheimer's disease

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Published online: 5 January 2012

The editorial by Moghbel and colleagues published in this issue of the *European Journal of Nuclear Medicine and Molecular Imaging* raises a number of concerns with regard to amyloid-beta (Aβ) imaging [1]. We appreciate the opportunity to address and clarify these concerns by referring to the scientific literature. There are several issues raised by Moghbel and colleagues which we acknowledge require careful consideration, further discussion, and research, including

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nonspecific white matter retention, the diagnostic value of Aβ imaging, and the role of Aβ pathology in disease generation. However, the editorial by Moghbel and colleagues brings into question the very feasibility of imaging Aβ in the brains of living humans [1]. Many of the issues raised in the editorial have been extensively researched and discussed in various scientific venues and publications over the past decade. However, it may be worthwhile to communicate these findings to a larger community, including scientists not active in this particular field of research. Thus, to avoid further misunderstandings and foster discussion based upon common grounds of knowledge in the future, we will try to address the issues raised by Moghbel and colleagues point by point and summarize the corresponding evidence in the following order: (1) alleged anomalies in the distribution of Aβ radiotracers, (2) perceived difficulties in visualizing Aβ plaques, (3) concerns about the binding properties of Aβ radiotracers to plaques, and (4) questions regarding the theoretical basis of Aβ imaging.

Alleged anomalies in the distribution of Aβ radiotracers

Moghbel and colleagues point out two issues regarding the regional distribution of Aβ radiotracers. One is a limitation of all existing Aβ radiotracers: nonspecific white matter retention. This phenomenon is well known, having previously been demonstrated in in vitro studies with human brain (see Fig. 4 of [2], Figs. 1C&D of [3], and Fig. 2 of [4]), in animal studies, (see Fig. 3 of [5]), and from the very beginning of in vivo human studies (see Fig. 3B of [4]). In hundreds of subjects, it has been shown that the level of this

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nonspecific white matter retention does not differ between Alzheimer's disease (AD) patients and normal controls [6–9]. Given that regional cerebral blood flow in white matter is approximately 40–50% of that in neocortex [10, 11], slower clearance of tracers [12] likely contributes to Aβ radiotracer retention in white matter [4, 13]. This nonspecific retention continues to represent a challenge to optimizing the analysis of Aβ imaging positron emission tomography (PET) data. It is true that spillover can occur from this nonspecific retention into neighboring gray matter (and vice versa when gray matter contains high amounts of fibrillar Aβ). However, it should be mentioned that due to the relatively small width of the cortical gray matter, which can be below the resolution of a PET scanner, the partial volume effect is not a problem unique to Aβ imaging but affects PET imaging procedures of the brain in general. Furthermore, in Fig. 2 of Moghbel et al., a representation of the partial volume effect is given that is not appropriate for Aβ imaging. Moghbel et al. refer to work in malignant lung lesions where the intensity differences are indeed huge and "overwhelming" [14]. In contrast, the typical retention of Aβ radiotracers in gray matter is not a small fraction of an overwhelming level of white matter retention as depicted, but at least comparable to threefold higher in typical Aβ-positive scans. Nevertheless, it is clear that the white matter uptake and the corresponding partial volume effects may lead to inaccuracies in the precise quantification of cortical tracer retention and thus assessment of cortical Aβ. While common to all Aβ radiotracers, this is more noticeable in currently published studies using ^{18}F-labeled Aβ radiotracers, which appear to generally show somewhat higher white matter retention as compared to ^{11}C-labeled Pittsburgh Compound-B (PiB) [4, 7, 9, 15–17]. However, this limitation has not proven to be a major hurdle to the quantitation of Aβ deposits in cortical gray matter, neither in the in vivo/postmortem cross-validation studies, nor in studies on the predictive value of the Aβ imaging findings, with regard to future cognitive decline. Nevertheless, there is room for further improvement in this context with regard to the development of tracers with less white matter retention and of image evaluation techniques (such as partial volume correction algorithms/volume of interest-based techniques for selective identification of gray matter uptake) [18–20]. Finally, it needs to be emphasized that for many clinical purposes, answering the question of the general presence of Aβ pathology in the brain with YES or NO by visual assessment will be of higher priority than absolute quantification and localization of these abnormalities. For example, in routine clinical practice, fluorodeoxyglucose (FDG) PET data of the brain are read without partial volume correction and the interpretation is usually established without absolute quantification of the findings.

A second alleged discrepancy between Aβ tracer retention and Aβ pathology—the claim that the frontal lobes do not harbor very high Aβ deposition in AD—is contradicted by a wealth of existing data. Thal et al. have clearly demonstrated heavy and early frontal Aβ deposition [21]. In their classic 2002 paper, this group (led by Heiko Braak) stated that in the earliest phase of Aβ deposition (phase 1) "*there are Aβ deposits in the frontal, parietal, temporal, or occipital neocortex*" [21] and Fig. 2 of this group's 1997 paper based on the examination of 2,661 brains clearly shows early and predominant basal frontal and anterior temporal Aβ deposition [22] (Fig. 1).

Numerous other neuropathological studies recapitulate these findings. In fact, the lead author of the paper that Moghbel et al. lean upon most heavily [23] later published a report showing that very high plaque density is found in the frontal cortex in AD [24]. An even more recently published work by this group demonstrated good correlation of an ^{18}F Aβ tracer to pathologically determined Aβ load in biopsies of the frontal cortex [25]. Despite the fact that neuropathological studies consistently detect a high Aβ plaque load in frontal cortex, neuropathological measures of percent plaque area are only semiquantitative and are complicated by variations caused by the fluorescence properties of the dyes used or secondary reactions used to amplify Aβ-antibody binding. Therefore, this may not be the most appropriate comparison to Aβ imaging. A more appropriate postmortem analysis would be truly quantitative assessments such as enzyme-linked immunosorbent assay (ELISA) analysis of Aβ load [26, 27]. In their benchmark study of 79 postmortem brains, Näslund et al. clearly show that frontal cortex typically contains two- to fourfold higher levels of total Aβ than temporal, entorhinal, parietal, or visual cortices [26]. In summary, the contention by Moghbel and colleagues that the frontal lobe is not a prominent site of Aβ deposition is inconsistent with the current state of knowledge regarding the neuropathology of AD.

The suggestion by Moghbel and colleagues that congophilic angiopathy (CAA) could be responsible for Aβ tracer retention in the frontal cortex also does not follow from the neuropathology literature. Several studies (including a recent one they cite [28]) clearly identify the occipital lobe as the site of highest Aβ deposition in CAA, but the occipital lobe is one of the lowest neocortical sites of Aβ radiotracer retention in AD [6, 29].

Moghbel et al. also claim that structural and functional changes such as regional atrophy, hypoperfusion, or hypometabolism should serve as a predictor of regional Aβ pathology. However, evidence that these processes are associated with regional postmortem Aβ pathology is sparse. For example, while brain atrophy may indeed occur in some areas of the brain affected by Aβ pathology, the data suggest that these abnormalities are sequential, and that Aβ deposition precedes synaptic dysfunction and neuronal loss [30–32], which are then evidenced as structural

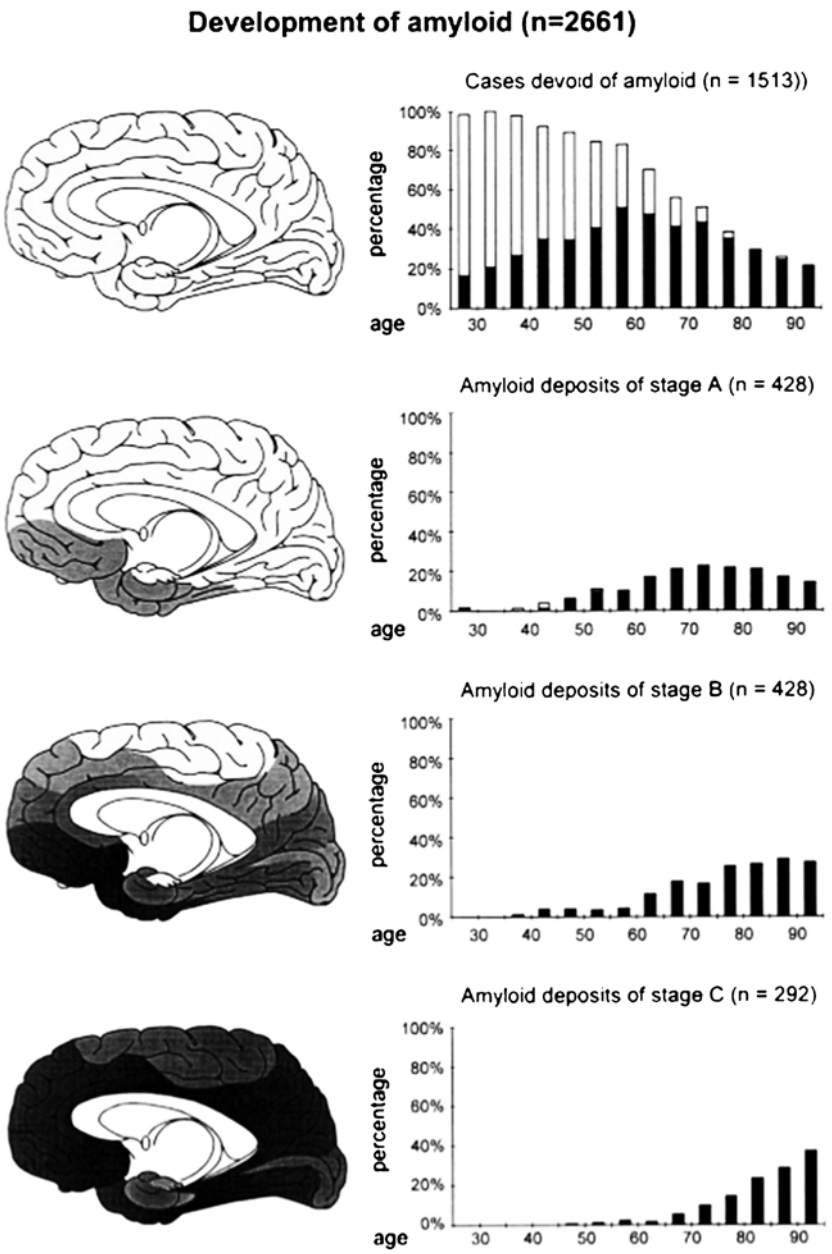

Fig. 1 "Development of amyloid deposits in 2,661 nonselected autopsy cases. The first line displays the frequency of cases devoid of changes in relation to the total number of cases in the various age categories. The second, third, and fourth lines are similarly designed, and show the evolution of the AD-related changes. The dark areas of the columns refer to subgroups showing the presence of neurofibrillary changes." (reproduced with permission from *Neurobiol Aging*, [22])

changes [33]. This may very well explain the regional discrepancies between patterns of atrophy and Aβ deposition detected by in vivo imaging studies [34]. At any rate, these considerations revolve around the interaction of different neurodegenerative pathologies and do not relate to the value of Aβ imaging to accurately measure the presence of Aβ in the brain.

The strongest proof of the feasibility of Aβ imaging to accurately measure Aβ deposition in vivo is founded on a wealth of detailed Aβ PET-neuropathology correlative studies that demonstrate the close match between in vivo Aβ radiotracer retention and postmortem Aβ pathology as assessed by ELISA, immunohistochemistry, Bielschowsky silver staining, or quantitative in vitro assessment of tritiated PiB binding [25, 35–43] (Fig. 2). Further support is added by the fact that high retention of Aβ radiotracers closely corresponds with: (1) low CSF Aβ levels, (2) presence of the apolipoprotein E ε4 allele, and (3) increasing age [44–47].

To make this argument even stronger, those subjects with a different regional distribution of Aβ in the brain such as those carrying one of the mutations associated with autosomal dominant AD [48–50], or familial British dementia [51], or subjects with posterior cortical atrophy [52–55] or CAA [56, 57] show a different regional distribution of PiB retention. If the retention of Aβ radiotracers was determined by nonspecific factors as much as Moghbel and colleagues suggest, then all scans would look relatively similar. The sharp distinction between the regional pattern of PiB

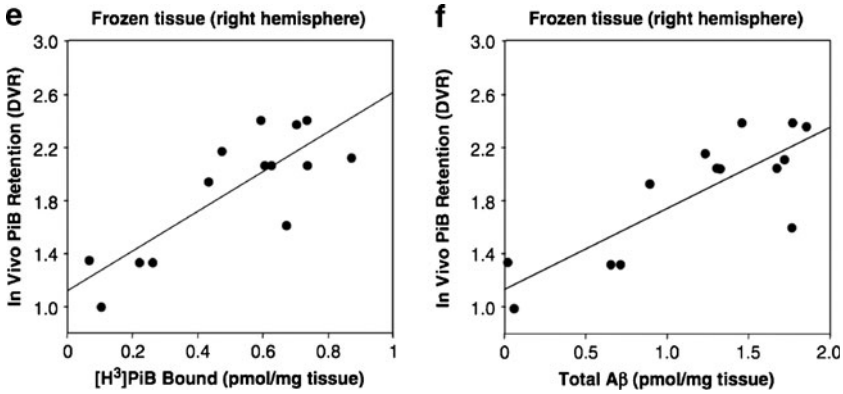

Fig. 2 Correlations of the in vivo PiB distribution volume ratio (*DVR*) values with postmortem quantifications of [^{3}H]PiB binding (*E*) and total insoluble Aβ ($Aβ_{1-40}$+$Aβ_{1-42}$) peptide levels (*F*) in 19 brain regions from fresh-frozen tissue from the right hemisphere of the same Alzheimer's disease subject. (reproduced with permission from *Brain*, [36])

retention in many presenilin-1 mutation carriers [48] and sporadic AD (Fig. 3)—corresponding to the known patterns of Aβ aggregation in their brains—makes a convincing argument for specific Aβ-driven retention of Aβ PET tracers.

Perceived difficulties in visualizing Aβ plaques

Moghbel and colleagues raise the concern that Aβ plaques in the brain are too small to allow in vivo imaging by means of PET. This argument would not only render Aβ imaging as impractical, but it would argue against the possibility of imaging structures/processes of even smaller size (i.e., molecular imaging in general), such as neuronal glucose metabolism (regularly imaged with FDG) or the receptor density on cell membranes. Aβ imaging does not attempt to resolve an individual 50–100 μm Aβ plaque. That futile effort would indeed be thwarted by the limited resolution of PET and the partial volume effects described. However, partial volume effects not only decrease the signal within a small structure such as a plaque due to low-signal bleed-in, but partial volume effects also increase the signal in the plaque penumbra by high-signal bleed-out. The net effect is a blurring of the signal on a submillimeter scale, but without significant loss of total signal on a larger scale. Like any other PET technique, Aβ imaging assesses the *average concentration* of Aβ radiotracer binding sites within a region of interest. Just as one dopamine receptor would be swamped by neighboring receptor-free tissue but millions of dopamine receptors produce a strong ^{11}C-raclopride signal in the striatum, also millions of fibrillar Aβ deposits produce a signal that is easily detectable in Aβ-laden parts of gray matter.

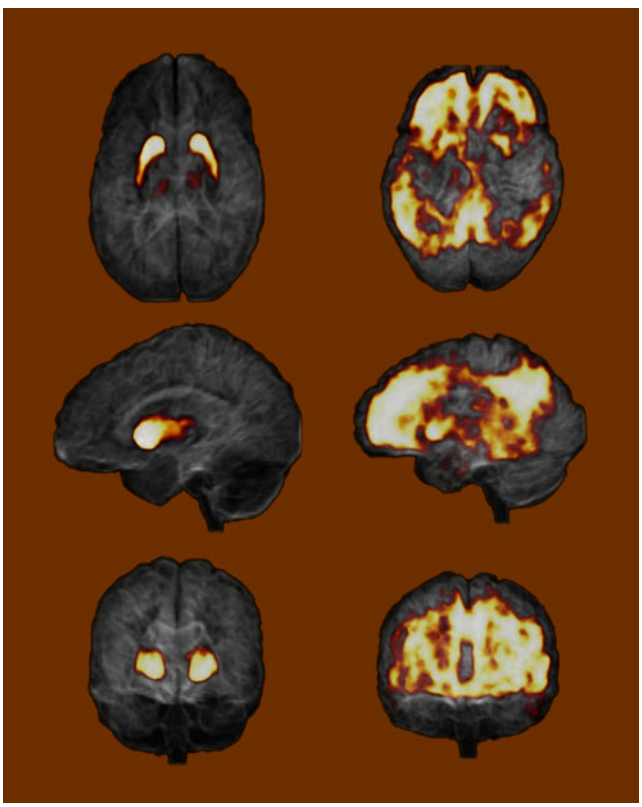

Fig. 3 Comparison of the regional distribution of PiB retention in a presenilin-1 mutation carrier (*left*) and a sporadic case of AD (*right*). The MRI is shown in *gray* and PiB retention is overlaid in a hot metal scale on transaxial (*top*), sagittal (*middle*), and coronal images (*bottom*)

Another concern brought up by Moghbel and colleagues is based on the surprising and unsupported assumption that the mass of Aβ in mild cognitive impairment (MCI) would be 60-fold less than (i.e., 1–2% of) that in AD, thus not possibly providing enough target structures for successful imaging. This assumption is not supported by data of neuropathological studies. In contrast, the quantitative postmortem data of Näslund et al. showed that subjects who die at the Clinical Dementia Rating (CDR) 0.5 stage (typically considered MCI) had an Aβ load 25–76% of that seen in patients with established dementia (CDR of 1.0 or greater) [26].

Even in groups of autopsy cases consisting of early or mild-moderate AD, neocortical amyloid markers are not significantly different when compared to those in MCI cases [58]. A recent review summarized the extent of amyloid pathology in MCI relative to cognitively normal people and early AD [59].

There is ample Aβ in the neocortex of AD and MCI patients and many normal controls to be detected with Aβ

radiotracers. The nominal concentration of Aβ in AD frontal cortex is ~3 μM [26, 27, 60], which is about twofold the number of PiB binding sites measured in vitro under saturating conditions [60] (and in the mid-nanomolar range under non-saturating conditions [61]). This is several orders of magnitude higher than the concentration of many receptors successfully assessed by PET. A recent paper demonstrated that, even under non-saturating conditions, there are about the same number of binding sites available in frontal and temporal cortex in postmortem human AD tissue [~60 fmol/mg tissue (~60 nM)]. The authors concluded that "*the observed binding of [^{11}C]PIB to amyloid plaques in vitro in human AD tissue, but not in healthy controls, is in correspondence with in vivo studies of patients with AD. This radiotracer is therefore very suitable in the early diagnosis of AD and can be used for the detection of pathological changes before there is a significant loss in cognitive function*." [61]. This, along with the high affinity of the PET radiotracers for Aβ, renders the concerns about visualizing Aβ plaques inconsistent with a wealth of existing data.

Concerns about the binding properties of Aβ plaques

Moghbel and colleagues also propose that there may be "*inherent difficulties of targeting fibrillar amyloid plaques, which are not as well-defined as the soluble forms of the protein*." Since the soluble (including oligomeric) forms of Aβ are not well defined at all, it is difficult to interpret this concern. In principle, conversion of a number of available binding sites from a soluble to a more solid or immobile status would be expected to increase the binding of a suitable ligand. For example, decreasing the mobility of receptors by fixation to a solid support can increase the binding of ligands [62, 63] because of decreased entropy and increased rebinding of small molecule ligands [64]. Currently, there are no data to support the idea that Aβ radiotracer binding to insoluble Aβ fibrils is fundamentally different than any other binding interaction of a radioligand with specific binding sites on other proteins (many of which are relatively immobile because they are embedded in membranes). In fact, the binding of Aβ radiotracers to Aβ fibrils shows typical, reversible binding properties in in vitro kinetic binding analyses [18].

The authors point out that no in vivo studies using high doses of unlabeled Aβ PET ligand to compete off the specifically bound Aβ radiotracer have been performed to validate the specific and reversible nature of binding in humans. This is true and will likely remain true for two reasons: (1) the nominal concentration of Aβ radiotracer binding sites is on the order of 1 μM in AD cortex [26, 27, 60], requiring micromolar levels of unlabeled ligand to effectively compete off the Aβ radiotracer; and (2) none of the Aβ tracers have been approved for human use at the doses required to achieve micromolar levels in brain. While it might be possible to perform such studies in animals, there are significant problems using Aβ radiotracers in transgenic mouse models of AD [60, 65], although some of these problems may be possible to overcome [66].

A more pertinent concern that Moghbel et al. correctly point out is that there are different tertiary forms of Aβ deposited in brain, such as the amorphous deposits in cerebellum which have very low affinity for all Aβ radiotracers. This conformational variability also may come into play in autosomal dominant forms of AD [48, 67] and in early stages of Aβ deposition [37], but the significance of non-fibrillar Aβ in typical, sporadic, late-onset AD is unknown. Studies assessing the selectivity of PiB for other aggregated misfolded proteins present in AD, such as tau/neurofibrillary tangles [36, 68] and α-synuclein/Lewy bodies [69, 70] utilizing in vitro methods that are more pertinent to PiB binding in vivo, have shown that in vivo cortical retention of ^{11}C-PiB primarily reflects fibrillar Aβ deposits. The potentially differential affinity of the Aβ tracers to various forms of Aβ deposits does not necessarily affect the clinical utility of Aβ imaging. For example, the case mentioned by Moghbel and colleagues [37] did not meet two commonly used sets of neuropathological criteria for AD [71, 72], because only sparse neuritic plaques and neurofibrillary tangles were present, although the case did meet the older Khachaturian criteria [73]. Nevertheless, it is important to keep in mind that different conformations of Aβ deposits in the brain [74] may affect the binding pattern of the tracers and that Aβ imaging modalities may not recognize all types of Aβ pathologies with equal sensitivity. This may be an interesting area of future research, to further improve the understanding of the quantitative information provided by in vivo Aβ imaging methods. However, any additional insights in this regard would rather lead to assigning a more specific information to the Aβ imaging signal than putting the general utility of this method into question.

Questions regarding the theoretical basis of Aβ imaging

Finally, Moghbel and colleagues broaden their concerns well beyond issues related to PET imaging by questioning the Aβ cascade hypothesis itself. This would imply that if Aβ deposition is not causative of AD, it is not worth measuring. In this context, it is important to draw a clear distinction between the value of Aβ imaging and the merits of the Aβ hypothesis—a hypothesis that remains supported by the bulk of existing data [75]. The basic feasibility of imaging AD pathology in vivo should not be confused with a discussion of the causal relevance of Aβ in AD. In isolation, Aβ imaging is not diagnostic, it is agnostic—that

is, agnostic to the role of Aβ deposition in AD. Aβ imaging was intended to assess the pathology of AD in vivo. This tool may ultimately be used to help prove or disprove the Aβ hypothesis of AD. The Aβ cascade hypothesis, though important, is not highly relevant to the feasibility and validity of Aβ imaging since, by definition, Aβ deposition remains a pathological hallmark of this disease.

Further, Moghbel et al. suggest that if Aβ deposition is causative, then the levels of Aβ in brain should correlate with cognition. Again, Aβ imaging is not a tool to assess cognition. In contrast, it may represent a tool to detect Aβ pathology independently and in particular before the onset of clinically significant cognitive symptoms. For example, a number of studies that have demonstrated the predictive value of Aβ pathology in subjects with MCI with regard to subsequent cognitive decline support this notion [76–79]. The long-recognized discrepancy between cognitive impairment and Aβ plaque burden in the brain [80] may be explained by three factors: (1) a dissociation in timing between early disease events and subsequent events that are more directly related to cognition [81]; (2) cognitive changes may be more related to the long-term, cumulative effects of soluble, oligomeric forms of Aβ (not apparent by routine neuropathology or imaged by current PET tracers) [82, 83]; and (3) the importance of cognitive reserve in the modulation of symptoms in the presence of brain pathology [84, 85].

Moghbel and colleagues further discuss the "*noteworthy rates of false-positive and false-negative PET scans using amyloid tracers*" [1]. This appears to reflect conceptual misunderstanding and terminological imprecision. A person with a positive Aβ PET scan who is negative for clinical AD should not be regarded as a "false-positive" but rather correctly classified as an "Aβ-positive" non-demented subject. This was clarified in the original report using PiB PET [4] as follows, "*Therefore, at the outset, it may be best to not equate amyloid deposition to clinical diagnosis. Rather than as a method of diagnosis, it might be best to first think of PiB retention more fundamentally as a method to detect and quantify brain β-amyloidosis, a term first used in reference to AD by Glenner* [86]." Aβ imaging simply detects cerebral β-amyloidosis. It does not provide a diagnosis by itself. It is only one tool to be used along with clinical assessment and other biomarker modalities to enhance our ability to provide earlier and more accurate diagnoses. The "false-positives" and "false-negatives" to which Moghbel et al. refer are mismatches between the presence of cerebral β-amyloidosis and symptoms of dementia. They are not false-positives and false-negatives for the presence of Aβ. The latter can only be determined by PET-neuropathology correlations and to date, there have been essentially no reported false-positives and only the rare false-negatives that would be expected when comparing an in vivo technique with a highly sensitive tissue stain [41, 87].

Summary

We acknowledge that there are a number of caveats with regard to the clinical value of Aβ imaging. This includes disorders other than AD which may show Aβ deposition (such as dementia with Lewy bodies), the unknown time to conversion in healthy Aβ-positive persons or the relative plateauing of the Aβ burden in later stages of disease [79, 87–90]. However, these caveats are not related to the proven functionality of the tracers and should not hamper the application and further evaluation of in vivo Aβ imaging with PET.

The fact that Aβ deposits can be detected by Aβ imaging in vivo is, in our opinion, a fact substantiated by a wealth of peer-reviewed data. ^{18}F-Labeled Aβ imaging radiotracers may be approved for clinical use in the near future. If so, this will be the first PET radiopharmaceutical developed commercially and the first PET tracer approved for clinical use by the US Food and Drug Administration (FDA) since FDG. As such, it represents a landmark moment in the field of molecular imaging and should encourage further commercial investment and development in the field. The functionality, sensitivity, and specificity of Aβ plaque imaging agents has by now been demonstrated in a level of detail and reliability (including in vivo-to-postmortem autopsy correlations) that has not been required or provided for most other imaging tracers clinically used today. Many of the concerns raised by Moghbel and colleagues in their current editorial in the *European Journal of Nuclear Medicine and Molecular Imaging* have been resolved previously, and we attempted to summarize the available information on these issues, to allow a future rational discussion on common grounds of knowledge. As is the case for any clinical test, Aβ imaging does not represent a perfect tool and some justified concerns remain, such as the nonspecific white matter retention or the effects of atrophy and partial volume on quantification. However, none of these concerns reasonably question the general feasibility of Aβ imaging or have been demonstrated to hamper the value of this procedure for detection of fibrillar Aβ pathology. A discussion regarding clinical indications for Aβ imaging is as welcome and important as the debate about the causal role of Aβ pathology in the genesis of AD. However, both of these topics clearly need to be treated independently from the feasibility of Aβ imaging itself. Thus, we believe that the remaining issues do not justify a call to slow the clinical development of these radiotracers and to withhold the availability of this technology from those it could potentially help. In contrast, we believe that hindering the progress of this exciting new molecular imaging approach could send an erroneous and discouraging signal to groups interested in the development of other new diagnostic agents. The inability to obtain the information provided by Aβ imaging would most certainly slow

down the urgently needed progress in understanding the basics of neurodegeneration and in the development of new approaches aiming to treat these devastating disorders. Aβ imaging has been repeatedly held up as one of the major successes of the past decade in the fight against AD. Thus, rather than to unnecessarily question the general feasibility of Aβ imaging, we believe we should vigorously foster the application of this unique new tool to improve our understanding of AD pathophysiology, to aid clinical diagnosis, and to advance the development of effective therapy.

Acknowledgments We wish to thank Prof. R. E. Indeer, M.D. and Dr. B. Oarsback, Ph.D. for inspiration and advice.

Conflicts of interest This response represents a consensus opinion of all coauthors, is meant to apply to all current amyloid PET tracers equally, and is not meant to favor any one particular tracer over any other. Two coauthors (WEK and CAM) have a conflict of interest based on being coinventors of an amyloid imaging tracer licensed by GE Healthcare, several coauthors (AD, MDI, KI, WJJ, KAJ, WEK, VJL, CLM, CAM, AN, RCP, EMR, CCR, RAS, KVL, VLV, and MWW) have been paid consultants to or received research grant support from one or more of the companies developing commercial amyloid imaging tracers (AstraZeneca, Bayer Schering, GE Healthcare Merck and/or Avid/Lilly) and one coauthor (DJB) holds a part-time position as a Senior Neurologist with GE Healthcare. Six coauthors have no conflicts of interest relative to amyloid PET tracers (BTH, CRJ, RAK, TJM, JCM, DJS).

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