Published in final edited form as:
Curr Opin Neurol. 2008 December ; 21(6): 683–687. doi:10.1097/WCO.0b013e3283168e1a.

The future of amyloid-beta imaging: a tale of radionuclides and tracer proliferation

William E. Klunk[a] and **Chester A. Mathis**[b]

a *Departments of Psychiatry and Neurology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA*

b *Departments of Radiology, Pharmacology, and Pharmaceutical Sciences, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA*

Abstract

Purpose of review—This review will focus on the coming proliferation of amyloid-beta imaging tracers and give an opinion on how the Alzheimer's disease field can develop a systematic means of evaluating which tracers are useful and how the useful tracers compare to each other.

Recent findings—Several new tracers have been reported to be useful for human amyloid-beta imaging. The most recent of these are labeled with fluorine-18. Compared with the 20 min half-life of carbon-11 used in the most widely used tracer, Pittsburgh Compound-B, the 110 min half-life of fluorine-18 allows for wider utilization in research and clinical settings.

Summary—It is likely that more than one fluorine-18-labeled tracer will come into common use. The use of preclinical and clinical 'bridging studies' to [C-11]Pittsburgh Compound-B could be a means to determine whether the sizable body of knowledge already gained in [C-11]Pittsburgh Compound-B studies can be applied to the understanding of these new tracers and to form a basis for the comparison among them. This approach could save resources and help sort out a potentially bewildering onslaught of new amyloid-beta imaging tracers.

Keywords

Alzheimer's disease; carbon-11; fluorine-18; mild cognitive impairment; Pittsburgh compound-B; positron emission tomography

Introduction

It feels a bit odd to be writing about the future of amyloid-beta (Aβ) imaging when the past history of this technology is brief, only about a decade old. However, this is a quickly evolving field fueled by both research and commercial interests and much has happened over the past 10 years. The field is at a crossroads and careful choices will be important to lead to a systematic and rigorous development strategy of new imaging tracers. These choices will have important implications not only for Aβ imaging, but also for antiamyloid drug development.

The first attempt to image brain Aβ deposition in Alzheimer's disease was reported by Friedland *et al*. [1] in 1997 using a monoclonal antibody fragment labeled with Tc-99m for

Correspondence to William E. Klunk, MD, PhD, University of Pittsburgh, Room 1422 WPIC of TDH, 3811 O'Hara Street, Pittsburgh, PA 15213, USA, Tel: +1 412 246 6460; e-mail: klunkwe@upmc.edu.

GE Healthcare holds a license agreement with the University of Pittsburgh on the basis of the technology described in this manuscript. Drs Klunk and Mathis are coinventors of PiB and, as such, have a financial interest in this license agreement.

single photon emission computed tomography (SPECT). Although this first attempt failed, it was instructive for subsequent efforts. The antibody fragment was too large to meet the stringent pharmacokinetic demands placed on an in-vivo neuroimaging agent. The limited brain uptake of this Fab fragment doomed the initial effort of imaging Aβ in living humans. The second attempt to image Aβ in the brain of Alzheimer's disease patients used PET and was presented in preliminary form by Barrio *et al*. [2] in 1999, and the first full report of this work appeared in 2002 [3]. This tracer is a fluorinated derivative of a nonspecific cellular membrane dye, 1,1-dicyano-2-[6-(dimethylamino)naphthalen-2-yl]propene (DDNP) called [F-18]FDDNP [4]. [F-18]FDDNP appears to have achieved some success as an Aβ imaging agent, but it has been sparingly utilized because of a relatively high background signal [5] and a relatively low specific binding signal [6] providing a limited dynamic range. In addition, there is limited experience with this tracer worldwide at present, as all published reports of human studies come from a single research group [3,6,7]. However, one important characteristic of [F-18]FDDNP is that it is labeled with the 110 min half-life positron emitter, fluorine-18. We will return to this topic in more depth below. The third report of human in-vivo Aβ imaging using a tracer now known as Pittsburgh Compound-B ([C-11]PiB) was presented in preliminary form in 2002 [8], with the full report in 2004 [9]. This tracer has been used in over 40 centers and 3000 participants around the world, including 22 sites in the United States and Canada, seven sites in Europe, ten sites in Japan and Korea and two sites in Australia, and it has been the subject of many independent reports (for a review, see [10]). A key feature of PiB relevant to this discussion is that it is labeled with the 20 min half-life positron emitter, carbon-11. The significance of this also will be discussed below.

Although [F-18]FDDNP was the first fluorine-18-labeled tracer and [C-11]PiB was the first carbon-11-labeled tracer, the results from human studies with at least nine other agents have been reported [11–17]. A task that is already upon the researchers who develop these tracers and will soon be upon the Alzheimer's disease field as a whole is that of separating the good, the bad and the indifferent on this growing list of Aβ imaging agents. In this review, we will suggest a time-honored approach for the evaluation of amyloid imaging tracers. From the outset, the overarching philosophy is that the future will see common use of more than one Aβ imaging agent. This eventuality will be fueled by developers of tracers using those tracers for their own research purposes as well as by commercial incentives that will bring more than one imaging company into the Aβ imaging arena in the same way that most drug classes have representation by several drug companies. Although a multiplicity of agents can lead to confusion, it is not necessarily a bad thing. A positive aspect of this is the fact that no one tracer is likely to hold all of the advantages and that accessibility to tracers will vary depending on whether they were developed in the academic or commercial realm. However, we are now at a point in the development of this field that we should establish some guiding principles that will promote good research practices and facilitate meaningful interpretation of results across tracers.

The first principle for acceptance of any Aβ imaging tracer must be that it effectively images brain Aβ deposits. To be effective, the quantity of tracer measured in a given brain area must be proportional to the amount of Aβ in that area and there must be sufficient signal-to-noise ratio to detect the tracer when the levels of Aβ have become clinically significant (i.e. the level would be detectable using current postmortem methodologies). These are both the most important and the most difficult criteria for a tracer to meet. There are published data for PiB demonstrating these properties in both postmortem and in-vivo studies [18–20]. It seems reasonable and necessary that when a claim is made for specific detection of any structure in human brain (normal or pathological), postmortem studies should be conducted with brain tissue that has been carefully characterized by independent and quantitative postmortem measures. For example, Aβ can be quantified biochemically by using an enzyme-linked immunosorbent assay [21], immunohistochemically by using antibodies specific for various

Aβ epitopes [22,23] or histologically using histochemical stains such as thioflavin-S [24], X-34 [25] or silver stains such as the Bielschowsky method [26]. Any tracer that is claimed to bind Aβ deposits *in vivo* should also bind to these structures in appropriately prepared postmortem tissue. This can be done in homogenates of frozen tissue using classic receptor binding approaches or in frozen tissue sections using quantitative autoradiographic techniques. The use of fixed tissue may not be appropriate for this purpose because of potential fixation artifacts. In addition to showing that the amount of tracer bound to brain tissue is proportional to the amount of Aβ in the tissue, this exercise can also yield indirect information on the specificity and sensitivity of the tracer. For example, a tracer with high white matter binding may not show proportionality with the amount of amyloid in the tissue due to a large influence of nonspecific white matter binding. Furthermore, one can begin to assess the amount of Aβ content required to give a specific binding signal at least twice that of the nonspecific background signal. This can be considered the 'best case scenario' for sensitivity, as many factors will conspire to reduce the sensitivity *in vivo*. The importance of quantitative homogenate binding or autoradiographic assays cannot be overemphasized. Demonstration of binding by qualitative autoradiographic techniques alone is not sufficient and proper quantitation of autoradiographs is a demanding process. There are several examples in the literature in which qualitative autoradiographic evidence of tracer binding to Aβ deposits did not predict success *in vivo* [12,27,28]. This may be because nonphysiological conditions are often used in these autoradiographic assays. In addition, the spatial resolution and signal-to-noise ratio that can be achieved with high-resolution microscopic autoradiography cannot be achieved during in-vivo PET or SPECT studies.

Of course, the *sine qua non* for the validation of an in-vivo Aβ tracer is the in-vivo–postmortem correlation study in humans. Autopsy cases can be difficult to acquire and the postmortem studies are demanding to perform in detail. Fortunately, the amount of Aβ (as determined by [C-11]PiB) does not change appreciably over 2 years during clinical Alzheimer's disease [29]. This means that Alzheimer's disease brain tissue obtained a year or more after the in-vivo study should be very informative with respect to the correlation of tracer retention and Aβ content of the tissue. Two in-vivo–postmortem correlation studies have been reported for [C-11]PiB and both showed excellent correspondence between the in-vivo and postmortem measures of Aβ [20,30]. No other Aβ tracer has yet been validated by correlation between in-vivo and postmortem data, but it is expected that these data will be forthcoming for some of the newer tracers.

A second principle for acceptance of any Aβ imaging tracer should be that it can be used reproducibly across many research and clinical settings. Most of the Aβ tracers mentioned above have thus far been used at only one or two sites. As mentioned above, [C-11]PiB is currently in use at more than 30 sites. Several tracers including [F-18]BAY94-9172 [31], [F-18] AV-45 [17], [F-18]AH110690 (or [F-18]3′F-PiB) [16], along with two compounds listed on clinicaltrials.gov called [C-11]AZD2995 and [C-11]AZD2184 (http://clinicaltrials.gov/ct2/show/NCT00692705) have recently been or soon will be employed in multisite phase II trials. Reproducibility across many sites is an indication of the robust nature of the tracer. Such independent validations are a time-honored part of the scientific process and will be a regulatory requirement for any commercial tracer. A byproduct of the use of a tracer at many sites is that the tracer will be studied in many participants. Despite thousands of participants having already been scanned with the most widely studied tracer, [C-11]PiB, we continue to learn more about the capabilities and limitations of this tracer, and a similar number of studies may be required of the other tracers before we have as good an understanding of their performance across a wide range of human studies. In addition, to fully understand the behavior of a tracer in neurodegenerative disease, the research population must be widened beyond Alzheimer's disease patients and controls. Studies on populations with mild cognitive impairment [32–35], early onset familial autosomal dominant Alzheimer's

disease [36–39], fronto-temporal lobar dementia [40–43], Parkinson's disease and dementia with Lewy bodies [42,44], cerebral amyloid angiopathy [45], prion disease and other atypical dementias [7,46] and, in particular, cognitively normal aging [33,47–52] have all greatly extended our understanding of Aβ imaging in general and, in particular, of the performance of [C-11]PiB in these special populations. It will be critical to gain similar broad experience with other useful tracers.

A third principle for acceptance of any Aβ imaging tracer must be that it is widely accessible and appropriate for the particular task at hand. It is this principle that brings us back to the discussion of carbon-11 and fluorine-18. The key difference between these radionuclides is their rate of decay or their decay 'half-life'. This physical parameter determines both how quickly the radiolabeled form disappears from the body and how far they can be distributed from the point of radiochemical production. The decay half-live of carbon-11 is approximately 20 min and that of fluorine-18 is approximately 110 min. Each has advantages. The main advantage of carbon-11 is that it decays so rapidly that sequential imaging studies in the same participant can be performed on the same day. For example, a 90 min [C-11]PiB study can be immediately followed by a study of cerebral metabolism using [F-18] fluorodeoxyglucose (FDG). This would require two separate days with a fluorine-18-labeled Aβ tracer paired with FDG. Another advantage of carbon-11 is that one can benefit from the wealth of experience already gained with [C-11]PiB by using that tracer. However, of the approximately 2000 PET scanner sites in the United States, only a small minority (<10%) have the on-site capability of producing high specific activity carbon-11-labeled products, and the situation is comparable worldwide. The majority of PET scanner sites rely on external production of fluorine-18 radiotracers (such as FDG) by regional cyclotron facilities that distribute the radiotracers to local scanners. The approximately 110 min half-life of fluorine-18 allows distribution within a 2–4 h travel radius. Thus, the need for a good fluorine-18 Aβ imaging tracer is mainly a matter of widening the availability (and thus making the tracer a commercially viable product as well). Most of the new Aβ tracers in the human study phases of development are labeled with fluorine-18. Because the properties of [C-11]PiB appear quite sufficient for imaging Aβ with a carbon-11 tracer, the goal seems to be finding a fluorine-18 tracer with performance characteristics similar to those of [C-11]PiB. This is very important to advancing the field of Aβ imaging, because the availability of a good fluorine-18 Aβ tracer will quickly increase the availability of this new technology by more than 10-fold.

So, how do we enter the future of amyloid imaging? It seems that the carbon-11-labeled tracer, [C-11]PiB, will continue to hold a particular niche in research centers with on-site cyclotron capabilities that are doing detailed imaging studies. In our opinion, the excellent signal-to-noise characteristics of [C-11]PiB and the wealth of validation studies and broad range of geographic and clinical experience make this the tracer of choice when one has the technical capabilities of producing it on-site. But how will we decide which of the many fluorine-18 Aβ tracers in development will serve a useful purpose both in research centers without carbon-11 capabilities and in clinical settings? How will we compare results from fluorine-18 tracers back to the wealth of data available from [C-11]PiB? If, as we predicted above, several fluorine-18-labeled Aβ tracers come into use, how will we compare results obtained from one with another? Will it be practical to expect each agent to be studied in as many patients, in as many different centers and in patients with as broad a clinical base as has already been done with [C-11]PiB before they can be approved for widespread use? Should we require several in-vivo–postmortem correlative studies prior to approval? These would not be completely unreasonable suggestions, but there is an alternative that has been suggested in the reports of several new tracers. The performance of these new tracers is often discussed in relation to the performance of separately published studies using [C-11]PiB. This is a logical way to proceed from the known to the unknown. However, it is often conducted in a nonrigorous manner, with no direct comparison ever performed.

That is, comparisons are being made in the absence of data. These comparative studies could readily be done for any new Aβ tracer. Detailed analysis of the binding properties of any new tracer could be quickly accomplished in homogenates of postmortem Alzheimer's disease brain. A classic cross-competition study using nonradioactive PiB to compete with radiolabeled test tracer and the corresponding experiment using nonradioactive test tracer to compete with radiolabeled PiB will give important data on whether the two tracers share a common binding site on Aβ and give a relative comparison of affinity. It is possible that a new Aβ tracer binds to a site on Aβ distinct from the binding site for PiB [53]. Unfortunately, these tracers will not be able to take advantage of the wealth of data already available for [C-11]PiB and it falls upon the developers of these tracers to produce an equivalent body of data to validate their tracer.

More important than the in-vitro comparisons, the short half-life of [C-11]PiB facilitates direct in-vivo comparison of this tracer to putative fluorine-18-labeled tracers. It is relatively straightforward to administer [C-11]PiB and follow this immediately with a fluorine-18-labeled Aβ tracer as is often done in same day [C-11]PiB/[F-18]FDG experiments. Having these direct comparison data could remove much of the necessity to acquire a large body of data similar to that already available for [C-11]PiB. To be sure, a sufficient body of new studies will be necessary to establish the safety and efficacy of each individual new tracer, but the number of studies, the number of sites involved and the types of patients studied could be lessened if one can be confident how the new tracer performs relative to the most widely studied tracer currently available. In addition, having this one piece of common ground (i.e. performance relative to [C-11]PiB) obviates the need to compare each new fluorine-18-labeled tracer directly to every other fluorine-18-labeled tracer in the same patients – an obviously impractical comparison to make.

Conclusion

In summary, as we look to the immediate future, we are on the verge of a proliferation of new Aβ imaging tracers. The majority of these will be fluorine-18-labeled tracers. This is fueled by the commercial and scientific need to expand the availability of this technology to the more than 90% of PET scanners that do not have the on-site capabilities to produce high specific activity carbon-11-labeled tracers. It is likely that more than one fluorine-18-labeled tracer will come into common use. The Alzheimer's disease field will need to develop a systematic means of evaluating which tracers are useful and how the useful tracers compare to each other. One approach would be to demand, for each new tracer, the assembly of a degree of preclinical and clinical experience similar to the best understood, currently used tracer, [C-11]PiB. Another method would be to use preclinical and clinical 'bridging studies' to [C-11]PiB as a means to determine whether the knowledge already gained in [C-11]PiB studies can be applied to the understanding of the new tracer and to develop a common ground among new tracers. This concept is not new. It is an established method of drug development after the establishment of an effective example in a given class of compounds. This approach could save resources and help sort out a potentially bewildering onslaught of new Aβ imaging tracers. Careful evaluation at this juncture will go a long way to ensuring that the future of Aβ imaging is long and productive.

Acknowledgements

Funding support for portions of the development program was provided by grants from The National Institutes of Health (R01 AG018402, P50 AG005133, K02 AG001039, R01 AG020226, R01 MH070729, K01 MH001976, R37 AG025516, P01 AG025204), the Alzheimer's Association (TLL-01-3381), GE Healthcare and the U.S. Department of Energy (DE-FD02-03 ER63590).

These funding agencies had no role in the design or interpretation of results or preparation of this article.

References

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 766–767).

1. Friedland RP, Kalaria R, Berridge M, et al. Neuroimaging of vessel amyloid in Alzheimer's disease. Ann N Y Acad Sci 1997;826:242–247. [PubMed: 9329695]
2. Barrio JR, Huang SC, Cole GM, et al. PET imaging of tangles and plaques in Alzheimer's disease with a highly hydrophilic probe. J Labelled Comp Radiopharm 1999;42:S194–S195.
3. Shoghi-Jadid K, Small GW, Agdeppa ED, et al. Localization of neurofibrillary tangles and beta-amyloid plaques in the brains of living patients with Alzheimer disease. Am J Geriatr Psychiatry 2002;10:24–35. [PubMed: 11790632]
4. Agdeppa ED, Kepe V, Liu J, et al. Binding characteristics of radiofluorinated 6-dialkylamino-2-naphthylethylidene derivatives as positron emission tomography imaging probes for beta-amyloid plaques in Alzheimer's disease. J Neurosci 2001;21:RC189. [PubMed: 11734604]
5. Noda A, Murakami Y, Nishiyama S, et al. Amyloid imaging in aged and young macaques with [11C] PIB and [18F]FDDNP. Synapse 2008;62:472–475. [PubMed: 18361444]
6. Small GW, Kepe V, Ercoli LM, et al. PET of brain amyloid and tau in mild cognitive impairment. N Engl J Med 2006;355:2652–2663. [PubMed: 17182990]
7. Boxer AL, Rabinovici GD, Kepe V, et al. Amyloid imaging in distinguishing atypical prion disease from Alzheimer disease. Neurology 2007;69:283–290. [PubMed: 17636066]
8. Engler H, Blomqvist G, Bergstrom M, et al. First human study with a benzothiazole amyloid-imaging agent in Alzheimer's disease and control subjects. Neurobiol Aging 2002;23:S429–S1429.
9. Klunk WE, Engler H, Nordberg A, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol 2004;55:306–319. [PubMed: 14991808]
10. Klunk, WE.; Mathis, CA. Amyloid imaging and (what is 'normal') aging. In: Jagust, W.; D'Esposito, M., editors. Imaging the aging brain. Oxford: Oxford University Press; 2008.
11. Verhoeff NP, Wilson AA, Takeshita S, et al. In-vivo imaging of Alzheimer disease beta-amyloid with [11C]SB-13 PET. Am J Geriatr Psychiatry 2004;12:584–595. [PubMed: 15545326]
12. Opazo C, Luza S, Villemagne VL, et al. Radioiodinated clioquinol as a biomarker for beta-amyloid:Zn complexes in Alzheimer's disease. Aging Cell 2006;5:69–79. [PubMed: 16441845]
13. Kudo Y, Okamura N, Furumoto S, et al. 2-(2-[2-Dimethylaminothiazol-5-yl]ethenyl)-6- (2-[fluoro] ethoxy)benzoxazole: a novel PET agent for in vivo detection of dense amyloid plaques in Alzheimer's disease patients. J Nucl Med 2007;48:553–561. [PubMed: 17401091]
14. Seibyl J, Jennings D, Koren A, et al. Clinical evaluation of 123-I IMPY as a beta-amyloid imaging biomarker in Alzheimer's subjects and controls. J Nucl Med 2007;48:57.
15. Rowe CC, Ng S, Mulligan RS, et al. First results from human studies of a novel F-18 PET ligand for brain β-amyloid imaging. J Nucl Med 2007;48:57.
16. Mathis CA, Lopresti B, Mason N, et al. Comparison of the amyloid imaging agents [F-18]3′-F-PIB and [C-11]PIB in Alzheimer's disease and control subjects. J Nucl Med 2007;48:56. [PubMed: 17204699]
17. Ichise M, Plett S, Joshi A, et al. Quantitative comparison of three novel 18F-labeled ligands for PET imaging of brain amyloid-β plaques in Alzheimer's disease. J Nucl Med 2008;49:214.
18. Klunk WE, Lopresti BJ, Ikonomovic MD, et al. Binding of the positron emission tomography tracer Pittsburgh compound-B reflects the amount of amyloid-beta in Alzheimer's disease brain but not in transgenic mouse brain. J Neurosci 2005;25:10598–10606. [PubMed: 16291932]
19. Maeda J, Ji B, Irie T, et al. Longitudinal, quantitative assessment of amyloid, neuroinflammation, and antiamyloid treatment in a living mouse model of Alzheimer's disease enabled by positron emission tomography. J Neurosci 2007;27:10957–10968. [PubMed: 17928437]
20. Ikonomovic MD, Klunk WE, Abrahamson EE, et al. Postmortem correlates of in vivo PiB-PET amyloid imaging in a typical case of Alzheimer's disease. Brain 2008;131:1630–1645. [PubMed: 18339640]

21. Golde TE, Eckman CB, Younkin SG. Biochemical detection of Abeta iso-forms: implications for pathogenesis, diagnosis, and treatment of Alzheimer's disease. Biochim Biophys Acta 2000;1502:172–187. [PubMed: 10899442]
22. Kalaria RN. The immunopathology of Alzheimer's disease and some related disorders. Brain Pathol 1993;3:333–347. [PubMed: 8293190]
23. Ulrich J. Histochemistry and immunohistochemistry of Alzheimer's disease. Prog Histochem Cytochem 1993;27:1–63. [PubMed: 7690493]
24. Guntern R, Bouras C, Hof PR, Vallet PG. An improved thioflavine S method for staining neurofibrillary tangles and senile plaques in Alzheimer's disease. Experientia 1992;48:8–10. [PubMed: 1371102]
25. Ikonomovic MD, Abrahamson EE, Isanski BA, et al. X-34 labeling of abnormal protein aggregates during the progression of Alzheimer's disease. Methods Enzymol 2006;412:123–144. [PubMed: 17046656]
26. Suenaga T, Hirano A, Llena JF, et al. Modified Bielschowsky and immunocytochemical studies on cerebellar plaques in Alzheimer's disease. J Neuropathol Exp Neurol 1990;49:31–40. [PubMed: 1688924]
27. Zhuang ZP, Kung MP, Wilson A, et al. Structure–activity relationship of imidazo[1,2-a]pyridines as ligands for detecting beta-amyloid plaques in the brain. J Med Chem 2003;46:237–243. [PubMed: 12519062]
28. Zhang W, Oya S, Kung MP, et al. F-18 stilbenes as PET imaging agents for detecting beta-amyloid plaques in the brain. J Med Chem 2005;48:5980–5988. [PubMed: 16162001]
29. Engler H, Forsberg A, Almkvist O, et al. Two-year follow-up of amyloid deposition in patients with Alzheimer's disease. Brain 2006;129:2856–2866. [PubMed: 16854944]
30. Bacskai BJ, Frosch MP, Freeman SH, et al. Molecular imaging with Pittsburgh Compound B confirmed at autopsy: a case report. Arch Neurol 2007;64:431–434. [PubMed: 17353389]
31. Rowe CC, Ackerman U, Browne W, et al. Imaging of amyloid beta in Alzheimer's disease with (18) F-BAY94-9172, a novel PET tracer: proof of mechanism. Lancet Neurol 2008;7:129–135. [PubMed: 18191617]
32. Kemppainen NM, Aalto S, Wilson IA, et al. PET amyloid ligand [11C]PIB uptake is increased in mild cognitive impairment. Neurology 2007;68:1603–1606. [PubMed: 17485647]
33. Pike KE, Savage G, Villemagne VL, et al. β-Amyloid imaging and memory in nondemented individuals: evidence for preclinical Alzheimer's disease. Brain 2007;130:2837–2844. [PubMed: 17928318]
34. Forsberg A, Engler H, Almkvist O, et al. PET imaging of amyloid deposition in patients with mild cognitive impairment. Neurobiol Aging 2007;29:1456–1465. [PubMed: 17499392]
35. Jack CR Jr, Lowe VJ, Senjem ML, et al. 11C PiB and structural MRI provide complementary information in imaging of Alzheimer's disease and amnestic mild cognitive impairment. Brain 2008;131:665–680. [PubMed: 18263627]
36. Klunk WE, Price JC, Mathis CA, et al. Amyloid deposition begins in the striatum of presenilin-1 mutation carriers from two unrelated pedigrees. J Neurosci 2007;27:6174–6184. [PubMed: 17553989]
37. Theuns J, Marjaux E, Vandenbulcke M, et al. Alzheimer dementia caused by a novel mutation located in the APP C-terminal intracytosolic fragment. Hum Mutat 2006;27:888–896. [PubMed: 16917905]
38. Remes AM, Laru L, Tuominen H, et al. Carbon 11-labeled Pittsburgh compound B positron emission tomographic amyloid imaging in patients with APP locus duplication. Arch Neurol 2008;65:540–544. [PubMed: 18413480]
39. Tomiyama T, Nagata T, Shimada H, et al. A new amyloid beta variant favoring oligomerization in Alzheimer's-type dementia. Ann Neurol 2008;63:377–387. [PubMed: 18300294]
40. Rabinovici GD, Furst AJ, O'Neil JP, et al. ^{11}C-PIB PET imaging in Alzheimer disease and frontotemporal lobar degeneration. Neurology 2007;68:1205–1212. [PubMed: 17420404]
41. Drzezga A, Grimmer T, Henriksen G, et al. Imaging of amyloid plaques and cerebral glucose metabolism in semantic dementia and Alzheimer's disease. Neuroimage 2008;39:619–633. [PubMed: 17962045]

42. Rowe CC, Ng S, Ackermann U, et al. Imaging beta-amyloid burden in aging and dementia. Neurology 2007;68:1718–1725. [PubMed: 17502554]
43. Engler H, Santillo AF, Wang SX, et al. In vivo amyloid imaging with PET in frontotemporal dementia. Eur J Nucl Med Mol Imag 2007;35:100–106.
44. Johansson A, Savitcheva I, Forsberg A, et al. [(11)C]-PIB imaging in patients with Parkinson's disease: Preliminary results. Parkinsonism Relat Disord 2007;14:345–347. [PubMed: 17855149]
45. Johnson KA, Gregas M, Becker JA, et al. Imaging of amyloid burden and distribution in cerebral amyloid angiopathy. Ann Neurol 2007;62:229–234. [PubMed: 17683091]
46. Ng SY, Villemagne VL, Masters CL, Rowe CC. Evaluating atypical dementia syndromes using positron emission tomography with carbon 11 labeled Pittsburgh compound B. Arch Neurol 2007;64:1140–1144. [PubMed: 17698704]
47. Mintun MA, Larossa GN, Sheline YI, et al. [^{11}C]PIB in a nondemented population: potential antecedent marker of Alzheimer disease. Neurology 2006;67:446–452. [PubMed: 16894106]
48. Edison P, Archer HA, Hinz R, et al. Amyloid, hypometabolism, and cognition in Alzheimer disease. An [11C]PIB and [18F]FDG PET study. Neurology 2006;68:501–508. [PubMed: 17065593]
49. Kemppainen NM, Aalto S, Karrasch M, et al. Cognitive reserve hypothesis: Pittsburgh Compound B and fluorodeoxyglucose positron emission tomography in relation to education in mild Alzheimer's disease. Ann Neurol 2008;63:112–118. [PubMed: 18023012]
50. Nelissen N, Vandenbulcke M, Fannes K, et al. Abeta amyloid deposition in the language system and how the brain responds. Brain 2007;130:2055–2069. [PubMed: 17586869]
51. Fotenos AF, Mintun MA, Snyder AZ, et al. Brain volume decline in aging: evidence for a relation between socioeconomic status, preclinical Alzheimer disease, and reserve. Arch Neurol 2008;65:113–120. [PubMed: 18195148]
52. Aizenstein HJ, Nebes RD, Saxton JA, et al. Frequent amyloid deposition without clinically significant cognitive impairment among the elderly. Arch Neurol. (in press)
53. Ye L, Morgenstern JL, Gee AD, et al. Delineation of positron emission tomography imaging agent binding sites on beta-amyloid peptide fibrils. J Biol Chem 2005;280:23599–23604. [PubMed: 15855161]