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Mapping Brain β -Amyloid

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Abstract

Purpose of review: This article reviews recent developments in the field of amyloid imaging using positron emission tomography (PET), specifically the ability to quantify the amount and distribution of brain A β , the protein that occupies a central position in leading theories of the pathogenesis of Alzheimer's disease (AD).

Recent Findings: Several imaging-pathology correlations place the technique itself on a stronger footing by showing good agreement between *in vivo* and histological measures of A β deposition. Correlations between A β and other measures of dementia – cognition, brain atrophy, and glucose metabolism – appear to support a view that A β triggers a host of downstream alterations that are closely related to dementia severity and progression. However, associations between PET measures of β -amyloid and cognition are generally fairly weak. The implications for clinical use are still uncertain. It seems likely that amyloid imaging will be useful for differentiating dementias associated with A β from those that are not, but the utility of this approach will depend on the availability of effective A β -directed treatments. Similarly, amyloid imaging offers the potential for predicting which non-demented individuals will eventually develop AD although here again the measurement of downstream A β effects may be important.

Summary: The ability to quantify the onset and progression of A β pathology in the brain offers the potential for investigating a host of questions concerning individual and neural vulnerability and the amyloid hypothesis of AD itself. These findings will have important basic and clinical implications.

Keywords

PET; amyloid; imaging; A β ; dementia; aging

The development of techniques to measure brain deposition of β -amyloid has opened a new era in aging and dementia research. While the role of A β in the pathogenesis of the most common dementia, Alzheimer's disease (AD), is still debated, many current theories of causation place this protein in a central role. Thus, the ability to non-invasively quantify the amount and distribution of A β with positron emission tomography (PET) offers new ways of addressing questions of both a basic and clinical nature.

Background

A number of radiopharmaceuticals are currently in use or under development as PET tracers for β -amyloid detection. The major positron-emitting radionuclides in clinical imaging

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are ^{11}C and ^{18}F with half-lives of 20 and 110 min, respectively. PET tracers for β -amyloid detection that utilize both PET radionuclides currently exist. Undoubtedly, the most widely used tracer is [^{11}C]2-(4'-methylaminophenyl)-6-hydroxybenzothiazole, known as Pittsburgh Compound B or PIB¹. Other ^{11}C compounds that have been used in human imaging include [^{11}C]BF-227² and [^{11}C]SB-13³. The most widely used ^{18}F labeled compound is [^{18}F]DDNP⁴, which binds to both β -amyloid and tau⁵ as well as other abnormal brain proteins including prion protein^{6,7}. This tracer does not seem to have the same target to background uptake as does PIB⁸. In addition, [^{18}F]BAY94-9172⁹ has binding properties similar to PIB and along with several other ^{18}F compounds under development, may provide information on β -amyloid deposition without the need for a local cyclotron. Nevertheless, the remainder of this review will largely focus on data obtained using [^{11}C]PIB since that tracer has received the most use.

A substantial amount of *in vivo* data supporting the use of PIB as an A β imaging agent has become available over the past few years. Studies have demonstrated that PIB not only binds to neuritic plaques, but also to diffuse plaques and cerebral amyloid angiopathy (CAA) as well as to tau and α -synuclein proteins, though for these latter two proteins binding is too low to be apparent in PET studies^{10,11}. *In vitro* binding of both 6-CN-PIB (which is more fluorescent than the parent compound) and [^3H]PIB are highly correlated with immunohistochemical assays of A β 40 and A β 42¹². In addition, a case report showed high correlation between the regional retention of PIB in a PET scan and a variety of postmortem measures of A β measured at autopsy¹². Another study reported good agreement between the presence of A β taken from frontal cortex biopsies at the time of intracranial pressure monitoring, and PIB retention in most regions of cortex¹³. These studies, and more which will be reported in the coming years, provide good imaging-pathological evidence supporting the use of *in vivo* A β imaging.

Important Observations in Aging, MCI, and AD

While amyloid imaging studies have found on average the highest uptake of tracers in AD patients, lowest uptake in normal older people and intermediate values in MCI patients^{5,14}, there is now more information available on the significance of these findings. Most importantly, the variability in tracer uptake, especially within normals and MCI patients, provides information that may help to understand the boundaries between aging and dementia and the clinical prediction of decline. Since its initial application, for example, it has been clear that while MCI patients as a group show PIB retention intermediate between AD and normals, subjects tend to resemble either AD patients or controls in terms of overall scan appearance and PIB retention¹⁵. While true prospectively analyzed data are not yet available, data indicate that MCI patients with higher PIB accumulation are at greater risk of progressing to AD¹⁶.

An important application of amyloid imaging is the study of cognitively normal older people. Because of the well recognized findings of AD neuropathology in cognitively intact elders¹⁷, it is not surprising that PIB imaging shows tracer retention in a moderate proportion of such individuals¹⁸. Some data suggests that PIB uptake is associated with reductions in episodic memory ability and other cognitive functions^{19,20}, although at least one study did not detect any cognitive differences between normal PIB+ and PIB- individuals²¹. While there are a number of methodological reasons for possible discrepancies, especially the method of defining PIB "positivity", it is also possible that cognitive deficits in this group of subjects are generally mild and mediated by "downstream" damage. For example, one study found strong relationships between PIB uptake and hippocampal atrophy in normal old people. This hippocampal atrophy in turn mediates memory failure, suggesting that β -amyloid effects on the brain are indirect via "downstream" pathology²². Another study identified MR-detected cortical thinning in AD-affected regions in normal older people who showed PIB retention²³. Similarly, mitigation of A β effects by cognitive reserve is another mechanism that might

moderate relationships between amyloid and behavior. Although limited data for this exist, findings that more highly educated individuals have greater PIB uptake despite similar levels of education²⁴, and that education mediates the relationship between PIB uptake and cognitive function support this view²⁵. The idea that β -amyloid affects the brain and cognitive function indirectly has important consequences for clinical and basic research. Studies of the relationships between PIB and cognition and other brain imaging methods and biomarkers provide an approach to further evaluating effects of A β on the brain.

Despite obvious interest, the association between β -amyloid deposition and cognition has not been widely studied, and results are inconclusive. An early report found relationships between memory function and PIB uptake, but this association was driven by AD subjects with no PIB uptake²⁶. Two additional studies^{14,27} found similar results – when normals, MCI and AD patients were combined, cognitive measures were related to global measures of PIB uptake, but when groups were analyzed separately there was no association. Another large series found associations between PIB and memory function for all 3 groups of subjects together, but also for the MCI and normal subjects separately – though not for AD subjects alone¹⁹. The authors concluded that there was a different relationship between amyloid and cognition in non-demented and demented individuals. Another longitudinal study found relationships between MMSE score and regional PIB DVR values at baseline, but not at follow up; in this study there was also no evidence of increased PIB accumulation over time²⁸. Another AD study found an association between PIB and the Clinical Dementia Rating scale (CDR)²⁹. These associations were relatively small (explaining 10-20% of the variance) and predominated in frontal cortex. In MCI, one study has found associations between PIB retention and measures of memory in MCI patients¹⁶.

Can the association between amyloid imaging and cognition be explained further by the relationships between β -amyloid deposition and other imaging biomarkers? Initial observations noted inverse relationships between PIB retention and glucose metabolism in AD patients in posterior brain regions (parietal and temporal cortex) but not in frontal regions^{1,26}. These findings may not be the same in MCI, as no relationship between PIB retention and glucose metabolism was seen in one study¹⁶. Furthermore, not all studies even in AD have confirmed these associations; one study noted inverse associations between FDG and PIB in temporal and parietal cortex when normals, MCI and AD patients were analyzed together, but not when groups were analyzed separately³⁰. Longitudinal data add to the confusion somewhat as subjects showed reductions in glucose metabolism over two years but not increases in PIB retention even though parietal lobe PIB and glucose metabolism were inversely associated at both baseline and follow up²⁸. Interestingly, this study contained a number of AD patients with low levels of PIB uptake and relatively high glucose metabolism.

Finally, there are some interesting data relating amyloid accumulation to MR measures of brain atrophy as well. In one study that carefully evaluated the topographic distribution of PIB and atrophy, it is clear that concordance between regional β -amyloid accumulation and atrophy exists in temporoparietal cortex, while frontal cortex shows β -amyloid accumulation without atrophy in AD and the medial temporal lobes show atrophy without PIB retention²⁷. These findings are similar to the PIB-glucose metabolism findings. As noted, regional cortical thinning in brain regions typically affected by AD can be detected even in normal older people with PIB evidence of β -amyloid deposition²³.

It seems likely based on the preponderance of evidence, that the relationship between β -amyloid deposition and cognition is at best relatively weak in AD patients though perhaps stronger in earlier disease stages. It is possible that A β deposition reaches a threshold or plateau, after which continued accumulation is difficult to detect. Studies that detect associations are generally those that evaluate patients with a wide range of PIB DVR values, often including

normal control subjects or individuals with MCI or AD with no PIB uptake. Furthermore, it seems that associations with cognition are stronger for other imaging markers such as both glucose metabolism and regional brain atrophy. This evidence paints a picture showing that the effects of A β are largely mediated by downstream brain changes that have a closer association with cognition. These changes include both neural pathology and synaptic dysfunction that are better measured with MRI and FDG-PET than with amyloid imaging.

Clinical Applications

Brain measurement of A β deposition has obvious clinical applications including both the diagnosis of dementia and prediction of decline. One obvious use of PIB is to differentiate dementias associated with β -amyloid from non-amyloid dementias. Frontotemporal dementia is a primary example of this, and several studies have now examined this disorder in comparison to AD^{31,32}. While these studies have generally shown that most FTLT patients do not demonstrate PIB uptake, exceptions are notable in both published series. These cases may represent incorrect clinical diagnosis or the co-occurrence of two separate pathologies. The relatively young age of the subjects, and the presence of AD-like glucose metabolic patterns in some of the PIB+ subjects, argues more in favor of the former than the latter interpretation.

PIB imaging has also been applied to atypical and unusual cases of dementia, including patients with language abnormalities. A series of patients with semantic dementia (SD) showed some similarities between SD and AD patients in patterns of glucose metabolism, whereas PIB uptake was notably absent in the SD group³³. While a case report of a patient with primary progressive aphasia (PPA) suggested an asymmetry of PIB uptake in the left hemisphere³⁴, a subsequent larger series of PPA patients made the observation that while FDG was asymmetric (with hypometabolism generally in the left hemisphere), PIB uptake was not³⁵. Furthermore, this study observed that patients with logopenic aphasia were more likely to show PIB uptake than those with other syndromes, a finding that was predicted based on the pattern of regional atrophy on MRI that is similar to AD³⁶.

PIB also has now been shown to detect in vivo imaging evidence of CAA. A recent report of a group of nondemented individuals diagnosed with CAA based on biopsy or MR findings showed PIB uptake that was intermediate between AD patients and normals, and which was especially prevalent in the occipital lobes consistent with the known pathological predilection of this pathology³⁷. These data also agree with both an earlier case report indicating that CAA was the dominant source of PIB signal in an autopsy-evaluated patient³⁸, and with in vitro data showing PIB binding to CAA¹⁰.

Studies of non-AD dementia syndromes associated with movement disorders have resulted in several interesting observations. A study of patients with Parkinson's disease and dementia (PDD) found increased cortical PIB binding in some subjects, similar to that seen in AD. However, other PDD subjects showed PIB uptake in brainstem, which was interpreted as reflecting binding to Lewy bodies³⁹. An in vitro report from another group, however, showed low affinity of PIB for α -synuclein and lack of PIB binding to A β -free diffuse Lewy Body brain homogenates⁴⁰, raising the possibility that brainstem binding in these subjects was non-specific. The presence of cortical PIB uptake in PDD is an interesting finding, however, that has been seen in a number of other studies. Cortical PIB uptake appears to be least common in patients diagnosed with Parkinson's disease, a bit more common in PDD, and more common still in those diagnosed with Dementia with Lewy Bodies (DLB)⁴¹⁻⁴³. PIB positive patients with movement disorders have also been found to be similar to AD patients in terms of CSF A β ₁₋₄₂ levels and ApoE4 allele frequency⁴⁴. These data support the view that subgroups of patients with movement disorders and dementia have A β brain pathology that can now be detected during life.

Basic Neuroscience

The ability to measure the deposition of β -amyloid in living people offers a unique method for understanding whether or how this protein is pathogenic. In one interesting series of studies, investigators have shown associations between regions that retain PIB, and brain regions that are highly active at rest or which are active during both rest and specific cognitive tasks as seen with fMRI studies^{45,46}. These data are congruent with the observation that synaptic activity regulates the levels of A β in interstitial fluid through the release of A β with synaptic exocytosis⁴⁷. This has generated the interesting hypothesis that specific neural systems are more vulnerable to β -amyloid deposition than others because of higher levels of brain activity. While this hypothesis might explain individual vulnerability to the development of β -amyloid pathology, the underlying cause of individual differences in resting state activity is unclear.

The question of an inflammatory response to A β has also been investigated with imaging methods. The PET tracer [¹¹C]PK11195, developed as a peripheral benzodiazepine receptor, binds to these receptors which are expressed on activated microglia. Two reports from the same research group have found increases in binding of this tracer in both patients with AD⁴⁸ and MCI⁴⁹. An interesting, yet unexplained, observation is that there was a regional association between PIB and PK11195 binding in AD, suggesting a relationship between A β deposition and inflammation, but this relationship was not seen in the MCI patients. A third study from a different group failed to detect increases in PK11195 in AD or MCI patients and noted no association between PIB and this marker of inflammation⁵⁰. While a host of methodological factors might explain this pattern of results it is also possible that inflammation is not detectable until relatively late stages of the disease.

Another area of investigation is the relationship between genetic abnormalities and A β deposition. An initial paper in 2007 reported the unusual finding of high levels of striatal PIB uptake in patients and asymptomatic carriers from 2 families with presenilin 1 mutations (one C410Y, the other A426P)⁵¹. A similar finding has been reported in a group of AD patients with a variant form of AD characterized by spastic paraparesis and deletion of exon 9 (PS-1 Δ E9)⁵², and also in two patients with CAA and duplication of the amyloid precursor protein locus⁵³. While these individuals also showed PIB uptake in cortex, especially posterior cingulate and precuneus, the striatal uptake was a particularly unusual feature. The reason for this pattern is currently unknown, but these cases also raise questions about the reasons for regional susceptibility to A β pathology.

Conclusions

While both clinical and basic applications of amyloid imaging are apparent, the primary utility of this technique is likely to be related to how clearly it can address the importance of A β in the pathogenesis of AD. In this regard the opportunities are exciting, and important new data are emerging. These data appear to support the view that amyloid precipitates a cascade of events that can be measured using other imaging technologies such as MRI and FDG-PET. While A β itself has an uncertain association with dementia severity, A β deposition is associated with regional atrophy and metabolic changes that are themselves strongly linked to dementia. This of course has major implications for clinical use. It seems likely that the presence of A β in the brains of cognitively normal individuals or those with MCI should predict subsequent decline, and longitudinal studies will soon begin to clarify this question. However it is also possible that the brain's response to this pathology – again as evidenced by atrophy or functional changes – may complicate this relationship and at the same time provide useful prognostic information.

With regard to clinical practice, future developments are likely to include the availability of amyloid imaging agents labeled with ^{18}F . This will result in the commercial availability of amyloid imaging, and potentially more widespread application. Of course, this must go hand-in-hand with results of clinical trials that support the utility of such an approach. While diagnosis and prediction are laudable goals, their importance will be driven by the availability of effective treatments. In fact, the development of drugs targeted against A β may be facilitated through amyloid imaging.

The basic science insights that can be obtained with amyloid imaging include the possibility of a clearer assessment of the time course of A β deposition, and relationships between A β and other structural and functional changes in the brain. A key question in AD research – why individuals with similar levels of A β pathology can differ in cognitive impairment – may also be open to study. Fundamental questions about how and why certain neural systems are affected by β -amyloid may finally be tractable through the use of this approach. The ability to image the in vivo deposition of this protein that is central to AD will undoubtedly play a major role in clinical and basic research for years to come.

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