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In vivo human amyloid imaging

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Abstract

PET imaging agents such as Pittsburgh compound B (PiB) allow detection of fibrillar β-amyloid (Aβ) *in vivo*. In addition to quantification of Aβ deposition in mild cognitive impairment and Alzheimer's disease, PiB has also increased our understanding of Aβ deposition in older adults without cognitive impairment. *in vivo* Aβ deposition has been studied in relation to genotype, structural and functional brain changes, as well as alterations in biomarker levels. To date, several studies have reported changes in Aβ burden over time. This, together with investigation of the relationship between Aβ deposition and cognition, sets the stage for elucidation of the temporal sequence of the neurobiological events leading to cognitive decline. Furthermore, correlation of Aβ levels detected by PiB PET and those obtained from biopsy or postmortem specimens will allow more rigorous quantitative interpretation of PiB PET data in relation to neuropathological evaluation. Since the first human study in 2004, *in vivo* amyloid imaging has led to advances in our understanding of the role of Aβ deposition in human aging and cognitive decline, as well as provided new tools for patient selection and therapeutic monitoring in clinical trials.

Keywords

PiB; amyloid; aging; MCI; AD; cognition; MRI; FDG; pathology; human; brain

While amyloid plaques are one of the neuropathological hallmarks of Alzheimer's disease (AD)[1–3], they are also found in approximately 30% of nondemented older adults on postmortem evaluation [4, 5]. Since 2004, the PET radioligand ^{11}C-Pittsburgh Compound-B (PiB) has allowed *in vivo* quantification of fibrillar β-amyloid (Aβ) [6–9]. This review focuses on human amyloid imaging with PiB which, unlike the more recently developed ^{18}F-labeled amyloid tracers[10–12], has been used not only to quantify Aβ but also to evaluate the relationship of Aβ with cognitive performance, structural and functional brain changes, and biomarker levels.

Group Discrimination and PiB cutoff levels

Mean levels of fibrillar Aβ detected by ^{11}C-PiB PET differ by diagnostic group, with the highest PiB retention detected in individuals with Alzheimer's disease (AD) and the lowest in individuals without impairment in memory or other cognitive domains, the cognitively normal older adults (CN) [13–23] (Table 1). As compared to CN, higher PiB retention in mild cognitive impairment (MCI) and AD localizes to frontal, lateral temporal, and parietal regions [14, 16–19, 22, 23]. In addition, some studies also report higher PiB retention in

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occipital cortex and the striatum of cognitively impaired individuals [14, 16, 18, 22, 23]. A similar spatial distribution of Aβ localizing to frontal, lateral temporal and parietal regions, including the precuneus, [13, 20] is observed in a subgroup of CN individuals with elevated PiB retention.

Despite consistency in group differences in mean levels across studies, the generalizability of specific PiB retention values across studies is limited given differences in quantification methods and populations studied. On an individual level, a given PiB retention level may be observed in older adults in different diagnostic categories. For example, 10–30% of CN have elevated Aβ on *in vivo* amyloid imaging [13, 20, 21, 23, 24, 25, 26], a finding consistent with neuropathological studies[4, 5]. A bimodal distribution of PiB retention values is observed in MCI, with both CN-like and AD-like levels of PiB retention [19, 22, 23, 27]. Overall, 40%–61% of MCI have elevated PiB retention [10, 19, 21, 22, 27]. Furthermore, while higher PiB retention has been observed in 3 out of 19 reported cases of nonamnestic MCI [21, 27, 28], only a single study investigated PiB retention in MCI subtypes in detail[27]. Finally, the majority of older adults with AD have high PiB retention relative to controls [18, 22–24], but several cases with low PiB retention also have been reported [14, 18, 29–31]. Although some of these cases may represent atypical presentations of non-AD dementia, deficient or weak PiB binding in polymorphic Aβ or in diffuse Aβ plaques also may explain these findings [29, 30].

Given the group differences in PiB levels[14–23], the discriminatory diagnostic value of PiB PET on an individual level has been investigated. Although accuracy up to 96% has been reported for discrimination between CN and AD [19, 28, 32], accuracy appears lower for discrimination between CN and MCI (75%) and MCI and AD (70%)[19]. Interestingly, of the cortical regions, the middle frontal gyrus provided the best overall diagnostic classification [19]. Furthermore, ^{11}C-PiB PET may complement ^{18}F-FDG PET, a measure of glucose metabolism, in dementia imaging[28] as the joint use of these tracers has been reported to improve the accuracy of discrimination of AD from MCI [19].

Perhaps one of the most important questions for application of PiB imaging on an individual basis is the value of PiB retention that constitutes a significant elevation in Aβ load, i.e. what constitutes a PiB+ study. A number of approaches have been explored for determination of PiB retention values leading to optimal classification accuracy. These approaches include data driven methods such as outlier exclusion, cluster analysis or tertile separation and methods that incorporate clinical information in determining a PiB+ cutoff [13, 19–21, 24–26, 32–40]. The published PiB+ cutoffs range from 1.15 to 1.6 ratio units, using cerebellum as a reference region [13, 19–21, 24–26, 32–38, 41–44]. This broad range of PiB+ cutoff reflects not only the differences in the approaches used to derive such cutoff, but also differences in populations studied and in PiB quantification methods which range from dynamic modeling of distribution volume ratio and binding potential to simpler standardized uptake values. In addition, while many studies use global cortical measures of PiB retention to determine PiB+ cutoff values[20, 21, 24–26, 32, 33, 35, 36, 44], others incorporate all regional PiB values or use only PiB values from selected regions of interest[13, 19, 38, 41, 42]. As PiB+ cutoffs are likely to be used as an aid for diagnosis and prognosis and for participant selection for clinical trials, further investigation of PiB+ cutoff values in relation to Aβ levels in brain tissue and in relation to clinical outcomes is necessary. Additional characterization of what constitutes a neglible level of PiB retention is also needed to determine which individuals are likely to remain cognitively normal and to aid in differential diagnosis of dementing conditions[23, 45].

Amyloid Imaging and Prediction of Conversion

Overall, investigations of PiB retention and progression to AD support the role of Aβ in the pathogenesis of AD[46]. Over a follow-up of 2.4 (SD 1.3) years, higher PiB retention predicted conversion to AD in 9 of 159 CN with a hazard ratio of 4.82[47]. These findings are consistent with observations of elevated PiB retention in older adults who were initially cognitively normal but experienced cognitive decline as compared to those whose cognition remained intact on longitudinal follow-up [37].

Similarly, elevated PiB retention distinguishes between MCI individuals who convert to AD and those with MCI who remain stable. Across studies, 38% to 82% of PIB+ MCI converted to AD over 8 months to 3 years follow-up [15, 27, 38, 41], contrasting with up to 7% conversion rate in MCI with low Aβ load, i.e. PiB− MCI [27, 38]. PiB retention in MCI converters is comparable to AD patients[15]. Moreover, the rate of conversion to AD is variable with fast converters (defined as conversion to AD within 1 year of follow-up) representing 47% of PiB+ MCI who convert to AD [38]. MCI converters have higher PiB retention in posterior cingulate gyrus, with some studies also showing higher PiB retention in frontal, temporal and parietal cortices [15, 38, 41]. Longer follow-up investigations are needed to evaluate not only the rates of progression to MCI and AD but also to determine factors associated with rapid progression.

Amyloid Imaging and Cognition

Of cognitive domains, episodic memory has been the most strongly associated with PiB retention[21, 26, 31, 37, 48]. In cross-sectional studies, this correlation is typically detected only across two or more diagnostic groups [21, 31, 49]. The association between PiB retention and episodic memory across groups remains evident even after adjustment for global ^{18}F-FDDNP retention[49] which reflects both Aβ and neurofibrillary tangles[50]. Within a diagnostic group, the relationship between PiB retention and episodic memory is variable [21, 31, 48, 51], with results differing between cohorts.

Longitudinal studies investigating cognitive decline in relation to PiB retention in nondemented older adults demonstrate relationships between PiB retention and episodic memory, as well as tests of executive function, working memory, and even mental status[26, 48]. Changes in episodic memory over time are associated with PiB retention in frontal, lateral temporal, parietoccipital and striatal regions [26]. In one study, higher PiB retention was associated with steeper decline in verbal word list recall in initially cognitively normal older adults who showed cognitive decline over time but not in those who remained cognitively stable [37].

Although higher PiB retention is associated with greater rates of cognitive decline[26, 48], some individuals with elevated PiB retention appear to remain cognitively stable, at least over the short follow-ups conducted to date. Some investigators have hypothesized that individuals more resistant to Aβ pathology have greater cognitive reserve, measured by education level or American National Adult Reading intelligence quotient[33, 42, 52–54]. Individuals with elevated PiB retention and greater cognitive reserve have better neuropsychological performance than those with lower cognitive reserve [33, 42, 55], suggesting that cognitive reserve may be one factor contributing to cognitive resilience despite high Aβ.

Amyloid Imaging and Structural Brain Changes

Neurodegenerative processes associated with neuronal damage and synapse loss are presumed to underlie decreases in brain volume [24, 56]. Cross-sectional measures of

hippocampal volume (HV) complement PiB PET findings as low HV and high global PiB retention are seen in AD and high HV and low global PiB retention in CN [24]. Global and/or regional PiB retention has been associated with smaller HV in PiB+ CN [44], MCI [27, 48, 51], across CN and AD groups [57], and in older adults with subjective cognitive impairment[58]. Several reports also indicate higher global and/or regional cortical PiB retention in association with lower volumes in amygdala, frontal, parietal, and lateral temporal cortices [27, 57, 58]. Higher global and/or regional PiB retention has been also associated with lower whole brain volume in some cross-sectional and longitudinal studies [34, 59].

However, the relationship between PiB retention and longitudinal changes in brain volume is complex. Over 1 year follow-up, dissociation between the rates of volume decline and the rates of global PiB retention was observed across diagnostic categories [60]. At the same time, baseline global PiB retention in CN has been shown to predict volume decline in hippocampus, precuneus, temporal cortex as well as enlargement of the ventricles over 2.1 years [61]. Nevertheless, in nondemented older adults, volume decline in the decade preceding the PiB measurement is not associated with subsequent global PiB retention, suggesting that structural changes and Aβ may not be related until individuals progress further across the disease continuum [62].

In addition, when both HV and PiB retention were evaluated as predictors of cognitive performance in CN and PiB+ MCI, only HV remained significant, consistent with a model in which cognitive performance is initially driven by the neurodegenerative changes in the medial temporal lobe[51]. Further investigation of the interaction between brain volume changes and PiB retention in the setting of longitudinal studies will enhance our understanding of the temporal sequence of the neurobiological processes leading to cognitive decline and progression to AD. As explicated recently by Jack and colleagues [63], declines in hippocampal volume may be a later step in this sequence.

Amyloid Imaging and APOE ε4 and other AD Biomarkers

The APOE ε4 allele is a major susceptibility gene conferring increased risk for late onset AD [64–66]. PiB retention is higher in frontal, temporal, and parietal cortex, including posterior cingulate and precuneus [25, 67, 68], as well as basal ganglia[67] as number of ε4 alleles increases. APOE ε4 genotype is also associated with faster conversion of PiB+ MCI to AD[38]. Compared to older adults without a family history of dementia, higher PiB retention in regions typically affected in AD has also been observed in 50–80 year old family history positive adults, especially in those with a maternal history of AD [69]. On the other hand, individuals with APOE ε2 allele have been shown to have low levels of PiB retention[25], consistent with known protective effects of APOE ε2 allele on risk for AD[70, 71].

Reduced CSF $A\beta_{42}$ levels also appear to be a useful biomarker of AD[72–74], perhaps reflecting a “sink” effect of $A\beta_{42}$ containing plaques associated with limited transport of soluble brain $A\beta_{42}$ to CSF[35, 75]. Consistent with this hypothesis, an inverse relationship between PiB and CSF $A\beta_{42}$ levels has been observed [31, 35, 68, 76–78]. Although cross-sectional studies suggest that lower leves of CSF $A\beta_{42}$ may occur at an earlier age than PiB retention [25], the temporal sequence of CSF biomarker changes in relation to PiB remains to be determined through longitudinal investigations.

PET studies of glucose metabolism and cerebral blood flow have been used to investigate functional brain changes in relation to Aβ. As expected, negative correlations are observed between glucose metabolism and PiB retention in AD and in combined groups of AD and MCI patients[14, 18, 31, 79, 80]. However, in MCI alone, positive correlations with ^{18}F-

FDG were found in the anterior cingulate and posterior cingulate/parietal regions[79]. Furthermore, while cross-sectional studies reveal no clear correlation between ^{18}F-FDG and PiB in CN [79], both longitudinal decreases and longitudinal increases in regional cerebral blood flow in the years preceding the PiB measurement were observed in association with higher PiB[36], suggesting that attempts to preserve neural function can already be detected in nondemented older adults.

Longitudinal Changes in Amyloid Deposition

A critical contribution of amyloid imaging agents is the opportunity for investigation of the dynamics of Aβ deposition *in vivo*. Over up to 2.5 years of follow-up, no or limited increases in PiB retention were observed in AD [60, 61, 80], despite declines in brain volume and metabolism, and worsening cognitive performance [60, 61, 80]. To date, only a single study has reported longitudinal changes in Aβ deposition in nondemented older adults. Similar to AD, annual changes in PiB retention were small, with a median increase of 0.05 SUVR/year in CN and 0.03 SUVR/year in amnestic MCI[60]. As increases in PiB retention were comparable across diagnostic groups, a model contrasting slow increases in PiB retention with more rapid (and possibly later) changes in brain volume has been proposed[60, 63].

It has also been suggested that unlike older adults who remain cognitively stable, individuals who progress to cognitive decline have faster rates of Aβ deposition [81, 82]. As elevated Aβ can already be detected by PiB PET in the fifth decade [25], longitudinal imaging studies of asymptomatic adults followed since their 50's may be necessary to provide a better understanding of the early phases of *in vivo* Aβ deposition. Furthermore, concurrent examination of factors that modify the rates of Aβ deposition, together with the evaluation of the temporal sequence of Aβ deposition in relation to structural and functional biomarkers, are needed to elucidate the substrates of cognitive decline.

Amyloid Imaging and Neuropathology

Case reports of demented older adults and case series of normal pressure hydrocephalus patients who underwent brain biopsy have shown concordance between imaging and neuropathological evaluation of Aβ[6, 83, 84]. Larger imaging-neuropathological correlation studies are, however, needed to quantify the amount of Aβ in brain tissue that can be detected by PiB PET *in vivo*. In addition, although PiB has been shown to bind to fibrillar Aβ[6] recent reports showing deficient PiB binding in AD attributed to polymorphic Aβ or amorphous Aβ plaques[30, 85] highlight the need for continued imaging-pathology correlative investigation. Furthermore, as PiB PET also detects intravascular fibrillar Aβ[6–9], a better understanding of the contribution of cerebral amyloid angiopathy to the overall PiB signal, especially in asymptomatic older adults, is needed.

Conclusions

Despite major advances in the field of human amyloid imaging, many questions remain. Further investigation of PiB deposition in relation to cognition and cognitive change, as well as conversion to MCI and AD, is necessary to better understand the role of Aβ as an individual progresses along the disease continuum. In addition, identification of older adults with high levels of Aβ who after longitudinal follow-up remain cognitively normal will enhance our understanding of factors which may protect against cognitive decline. With more extensive imaging follow-up, PiB studies have the potential not only to clarify the dynamics of Aβ deposition but also - in conjunction with structural and functional biomarkers - to help elucidate the temporal sequence of events leading to cognitive decline. However, quantification of fibrillar Aβ detected by PiB and further study of the binding

properties of different forms of Aβ will be instrumental for more quantitative interpretation of PiB PET in relation to Aβ in biopsy or postmortem specimens. Finally, determination of the specific values for a PiB+ case has implications not only for research study design, including subject selection into clinical trials, but also for use as an aid to diagnosis and prognosis of individual patients.

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Table 1

values in older adults without cognitive impairment, with mild cognitive impairment, and those with Alzheimer's disease

Year	Design	Sample	#Subjects	Mean Age	Method	PiB in AD	PiB in MCI	PiB in CN	Findings
2007	Case control	AD, DLB, FTD, MCI, CN	17 AD, 10 DLB, 6 FTD, 9 MCI, 27CN	74 AD, 72 DLB, 71.5 FTD, 73 MCI, 72 CN	$DVR_{0–90r}$	• Mean=2 • Frontal=2.02–2.19 • LatTemp=1.9 • PCG=2.19 • Parietal=1.93	• Mean=1.6 • Frontal=1.45–1.71 • Parietal=1.49 • LatTemp=1.5 • PCG=1.72	• Mean=1.2 • Frontal=1.12–1.30 • Parietal=1.1 • PCG=1.27 • LatTemp=1.19	• Global / Regional: AD > CN (p>0.05) • Global / Regional: MCI > CN (p>0.05)
2008	Case control	AD, MCI, CN	17 AD, 13 MCI, 7 CN	72 AD, 72 MCI, 69 CN	$DVR_{0–90r}$	• MFG=1.92 • STG=1.67 • IP=1.82 • PCG=1.93	• MFG=1.5 • STG=1.36 • IP=1.48 • PCG=1.58	• MFG=1.16 • IP=1.19 • STG=1.15 • PCG=1.26	• Regional: AD > CN (p>0.05) • Regional: AD > MCI (p>0.05)
2005	Case control	AD, MCI, CN	5 AD, 5MCI, 5 CN	68 AD, 71MCI, 59CN	$DVR_{35–90r}$, also $SUVR_{40–60r}$,)	• Frontal=2.63, • Parietal=2.55, • PCG=2.63, • LatTemp=2.37	• Frontal=1.81, • Parietal=1.87, • PCG=1.93, • LatTemp=1.79	• Frontal=1.32, • Parietal=1.29, • PCG=1.24, • LatTemp=1.19	• Regional: AD > CN (p>0.05)
2006	Case control	AD, nondeme nted	10 AD (CDR>0), 41 CDR=0 (20 older CN mean age 77)	77AD, 65CN	$BP_{0–60r}$	• Mean=0.633		• Mean=0.098	• Global: AD > CN (p < 0.0001)
2004	Case control	AD, CN	16 mild AD, 9 CN	65 AD, 69 older CN, 21 young CN	$SUVR_{40–60r}$	• Frontal=1.56 • Parietal=1.45 • LatTemp=1.26		• Frontal=0.8 • Parietal=0.85 • LatTemp=0.83	• Regional: AD > CN (p < 0.006)
2008	Case control	MCI, AD, CN	21 MCI, 27 AD, 6 CN	63.3 MCI, 66 AD, 67 CN	$SUVR_{40–60r}$	• Frontal = 2.3 • Parietal=2.2 • Temporal=1.8 • PCG=2.2	• Frontal=1.6 • Parietal=1.7 • PCG=1.7 • Temporal=1.5	• Frontal=1.3 • Parietal=1.3 • PCG=1.4 • Temporal=1.3	• Regional: MCI converters > CN (p<0.01) • Regional: AD > MCI and MCI

Year	Design	Sample	#Subjects	Mean Age	Method	PiB in AD	PiB in MCI	PiB in CN	Findings
									nonconverters (p<0.01)
2007	Case control	AD, MCI, CN	31 AD, 33 MCI, 32 CN	75 AD, 71MCI, 72CN	$SUVR_{40–70r}$	• Mean =2.42	• Mean= 1.85	• Mean=1.4	• Global: MCI > CN (p<0.001) • Global: AD > MCI (p<0.001)
2006	Case control	AD, CN	17 AD, 11 CN	72 AD, 65 CN	$SUVR_{60–90r}$	• Frontal = 1.73 • Parietal=1.49 • PCG=1.81 • Temporal=1.52		• Frontal=1.06 • Parietal=1.02 • PCG=1.24 • Temporal = 1.05	• Regional: AD > CN (p<0.001)
2007	Case control	Amnestic MCI (aMCI), CN	13 aMCI, 14 CN	70 aMCI, 65 CN	$SUVR_{60–90rv}$		• Frontal = 1.5 • Parietal=1.49 • PCG=1.92 • LatTemp=1.59	• Frontal=1.08 • Parietal=1.14 • PCG=1.38 • LatTemp 1.24	• Regional: MCI > CN (p<0.01)
2007	Case control	AD, CN	19 AD, 14 CN	66 AD, 64 CN	$SUVR_{60–90rv}$	• Primary motor cortex = 1.7 • Primary sensory cortex = 1.76 • Primary visual cortex=1.63		• Primary motor cortex=1.26 • Primary sensory cortex =1.21 • Primary visual cortex = 1.63	• Regional: AD > CN (p<0.001)

urgh compound-B. AD: Alzheimer's disease. DLB: Dementia with Lewy bodies. FTD: Frontotemporal Dementia. MCI: Mild Cognitive Impairment. CN: Cognitively Normal. $DVR_{0–90r}$: me Ratio quantified over 90 minutes; ROI analysis. $DVR_{35–90r}$: Distribution Volume Ratio determined using data from 35–90 minutes; ROI analysis. $BP_{0–60r}$: Binding Potential 0 minutes; ROI analysis. $SUV_{40–60r}$ Standardized Uptake Value Ratio, quantified from 40 to 60 minutes; ROI analysis. $SUV_{60–90rv}$: Standardized Uptake Value Ratio, quantified from ROI and voxel based analysis. Mean: Mean cortical PiB retention (average of frontal, parietal, lateral temporal and in some studies occipital regions). LatTemp: Lateral temporal cortex. ngulate gyrus. MFG: Middle frontal gyrus. STG: Superior temporal gyrus. IP: inferior parietal lobe. Age was not rounded up.