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Molecular Imaging of Alzheimer Disease Pathology

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ABSTRACT

Development of molecular imaging agents for fibrillar β -amyloid positron-emission tomography during the past decade has brought molecular imaging of Alzheimer disease pathology into the spotlight. Large cohort studies with longitudinal follow-up in cognitively normal individuals and patients with mild cognitive impairment and Alzheimer disease indicate that β -amyloid deposition can be detected many years before the onset of symptoms with molecular imaging, and its progression can be followed longitudinally. The utility of β -amyloid PET in the differential diagnosis of Alzheimer disease is greatest when there is no pathologic overlap between 2 dementia syndromes, such as in frontotemporal lobar degeneration and Alzheimer disease. However β -amyloid PET alone may be insufficient in distinguishing dementia syndromes that commonly have overlapping β -amyloid pathology, such as dementia with Lewy bodies and vascular dementia, which represent the 2 most common dementia pathologies after Alzheimer disease. The role of molecular imaging in Alzheimer disease clinical trials is growing rapidly, especially in an era when preventive interventions are designed to eradicate the pathology targeted by molecular imaging agents.

ABBREVIATIONS: $A\beta$ = β -amyloid; AD = Alzheimer disease; DLB = dementia with Lewy bodies; MCI = mild cognitive impairment; NIA-AA = National Institutes of Aging and the Alzheimer's Association; PiB = Pittsburgh compound-B

The pathologic hallmarks of Alzheimer disease (AD) are neurofibrillary tangles of hyperphosphorylated τ and extracellular plaques of β -amyloid ($A\beta$) proteins, which involve the brain many years before the emergence of symptoms. Molecular imaging with agents that bind to $A\beta$ and τ proteins may detect the presence and progression of Alzheimer disease pathology during the preclinical stage when the disease course may be altered by early intervention. Imaging of the $A\beta$ pathology with PET has been used in clinical research settings for almost a decade and was recently approved by the US Food and Drug Administration for clinical use. Imaging of τ pathology with PET has been investigated less; however, its impact on understanding the pathophysiology of AD and on treatment planning would be significant. Imaging of both $A\beta$ and τ will likely contribute independently to early diagnosis, differential diagnosis, and the tracking of disease

progression during the preclinical, prodromal, and clinical stages of AD.

Detecting Preclinical and Prodromal AD Pathology with Molecular Imaging

During the past decade, discovery of $A\beta$ imaging with Pittsburgh compound-B (PiB)¹ PET provided a window into the pathophysiology of AD in living individuals. Although postmortem studies have long suggested a high prevalence of $A\beta$ pathology with moderate-to-frequent plaques reaching 47% in cognitively normal older adults, imaging of $A\beta$ pathology with PET provided an in vivo confirmation of this observation. The prevalence of PiB positivity ranges from 20% to 34% in independent cohorts of cognitively normal individuals.^{2–6} The variability is likely associated with the ascertainment of participants and the cutoff used for PiB positivity as well as the median age of the cohorts. For example, in a population-based study of cognitively normal older adults that included individuals with neurologic, psychiatric, or systemic illnesses, a representative sample of the population, the prevalence of PiB positivity was 31% with a global cortical PiB uptake cutoff of >1.5 , but the prevalence increased to 44% with a cutoff of >1.4 ,⁷ which is on par with the postmortem studies in community-based cohorts of cognitively normal elderly.⁸

Although $A\beta$ pathology is common in cognitively normal individuals, the harmful effects of $A\beta$ pathology on cognitive func-

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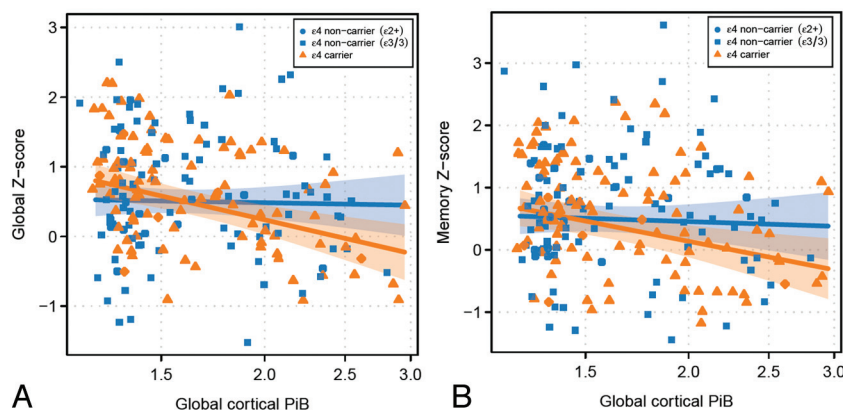


FIG 1. Associations between cortical PiB retention and standardized memory and global cognitive domain scores according to *APOE* $\epsilon 4$ status. Higher $A\beta$ load is associated with greater global cognitive impairment (partial $r_s = -0.18$; $P < .01$) (A) and memory impairment (partial $r_s = -0.14$; $P < .01$) (B). However global cognitive function in *APOE* $\epsilon 4$ carriers is influenced more by the $A\beta$ load compared with *APOE* $\epsilon 4$ noncarriers matched by age, sex, education, and $A\beta$ load (sequential ANOVA interaction; $P = .01$), suggesting that *APOE* isoforms modulate the harmful effects of $A\beta$ on cognitive function (A). A similar trend is seen with memory function (sequential ANOVA interaction; $P = .08$). Reprinted with permission from Kantarci K, Lowe V, Przybelski SA, et al. *APOE* modifies the association between Abeta load and cognition in cognitively normal older adults. *Neurology* 2012;78:232–40.⁵

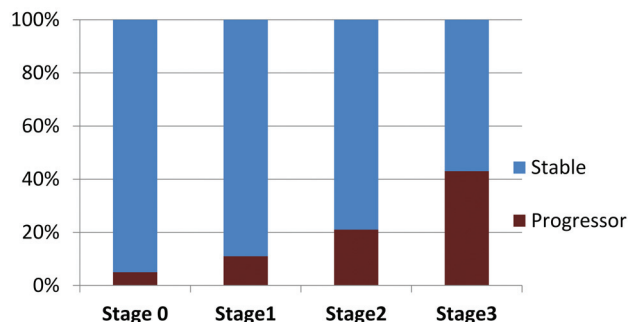


FIG 2. Preclinical staging of Alzheimer disease and short-term progression rates. If one used the preclinical staging criteria, at fixed cut-points corresponding to 90% sensitivity for diagnosing AD and the 10th percentile of cognitive scores of cognitively healthy individuals, stage 0 corresponds to a low $A\beta$ load on PET and the absence of imaging markers of neuronal injury (ie, normal hippocampal volumes on MR imaging and/or the absence of an AD-like pattern of hypometabolism on PET); stage 1 corresponds to a high $A\beta$ load on PET and the absence of imaging markers of neuronal injury; stage 2 corresponds to a high $A\beta$ load on PET and the presence of imaging markers of neuronal injury; and stage 3 corresponds to a low $A\beta$ load on PET, the presence of imaging markers of neuronal injury, and subtle cognitive impairment. The percentage of patients who progressed to mild cognitive impairment during a median follow-up of 15 months is demonstrated. The diagnosis of MCI was made according to the Petersen criteria,⁹⁰ blinded to the imaging biomarker data used for staging.

tion are modest.^{5,9–12} The risk of cognitive decline further increases with the $A\beta$ load.^{6,13,14} The high $A\beta$ load on PET appears to have subtle effects on memory, attention/executive function, and visual-spatial processing.^{5,6,10,13–18} The relationship between $A\beta$ load and cognitive domain functions does not appear to follow a specific functional-anatomic pattern but is localized to the frontal, lateral temporal, and parietal lobes; posterior cingulate; and precuneus cortex, independent of the cognitive domains that are affected.⁵ Therefore the effects of $A\beta$ detected on PET appear to be global, and the *APOE* $\epsilon 4$ status further modifies the association between $A\beta$ load and cognition.^{5,19} Although cognitively

normal carriers of the *APOE* $\epsilon 4$ have higher $A\beta$ loads on PET compared with noncarriers,^{3,5,20} when matched on $A\beta$ load, *APOE* $\epsilon 4$ carriers tend to perform worse on cognitive tests compared with noncarriers (Fig 1).⁵ Thus, *APOE* $\epsilon 4$ not only increases the risk for $A\beta$ deposition but also influences AD pathology by modulating the harmful effects of $A\beta$ on cognitive function through other potentially synergistic mechanisms, such as enhancing hyperphosphorylation of the τ protein²¹ and reducing choline acetyltransferase activity.²²

In 2011, the clinical diagnostic criteria for AD were revised under the auspices of the National Institutes of Aging and the Alzheimer's Association (NIA-AA).²³ These new guidelines included imaging markers in the diagnostic criteria for AD and proposed research criteria that included imaging evidence of AD for the diagnosis of preclinical AD.²⁴ The new criteria require evidence of $A\beta$ pathology of AD for the diagnosis of preclinical AD either through molecular imaging or CSF biomarkers. Any imaging or biomarker evidence of AD-related neurodegeneration measured with an AD pattern of atrophy on MR imaging or an AD pattern of hypometabolism on [¹⁸F] fluorodeoxyglucose PET and the presence of subtle cognitive difficulties in addition to the $A\beta$ pathology increase the stage of preclinical AD from 1 to 3.

The preclinical AD research criteria was operationalized in a population-based sample of cognitively normal older adults from the Mayo Clinic Study of Aging.²⁵ At fixed cut-points corresponding to 90% sensitivity for diagnosing AD and the 10th percentile of cognitive scores of cognitively normal individuals, 43% of the sample was classified as stage 0; 16%, stage 1 ($A\beta$ PET-positive); 12%, stage 2 ($A\beta$ PET-positive and neurodegeneration-positive on MR imaging or FDG-PET); and 3%, stage 3 ($A\beta$ PET-positive and neurodegeneration-positive on MR imaging or FDG-PET and subtle cognitive difficulties).²⁶ Furthermore, the proportion of subjects who progressed to mild cognitive impairment (MCI) or dementia increased with advancing stage (Fig 2).²⁷ However, 23% of the population did not fit the preclinical AD stages because they had normal $A\beta$ PET imaging findings but abnormal neurodegeneration biomarker study findings, which we classified as suspected non-AD pathophysiology. The suspected non-AD pathophysiology group is of particular interest because the individuals progress to MCI in the short term (10% in 15 months), albeit at a rate similar to that of subjects with stage 1 preclinical AD (11% in 15 months). The pathologic basis of positive neurodegeneration biomarker findings in the absence of $A\beta$ pathology in this cognitively normal group is under investigation.²⁸

According to the new guidelines by the NIA-AA, the prodromal stage of AD is characterized by mild cognitive impairment, and research criteria further classify patients with MCI as having MCI due to AD on the basis of biomarker evidence of AD pathophysiology. A recent study from the Mayo Clinic Study of Aging

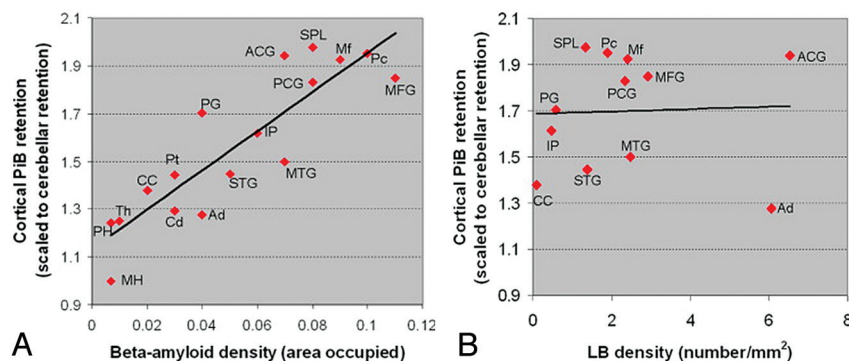


FIG 3. Correlations of cortical PiB retention and A β (A) and Lewy body (B) densities in individual brain regions of a case with dementia with Lewy bodies. There was a strong correlation between PiB retention and A β attenuation in the 17 ROIs that were analyzed on pathologic examination by using the Spearman rank-order correlation ($r = 0.899$; $P < .0001$). There was no correlation between Lewy body attenuation and PiB retention ($r = 0.13$; $P = .66$). MH indicates middle hippocampus; PH, posterior hippocampus; Th, thalamus; Cd, caudate; Ad, amygdala; CC, calcarine cortex; Pt, putamen; STG, superior temporal gyrus; MTG, middle temporal gyrus; IP, inferior parietal; PG, precentral gyrus; PCG, posterior cingulate gyrus; MFG, middle frontal gyrus; Mf, midfrontal; ACG, anterior cingulate gyrus; Pc, precuneus; SPL, superior parietal lobule. Reprinted from *Neurobiology of Aging*, Vol. 33(5), Kantarci K, Yang C, Schneider JA, et al. Antemortem amyloid imaging and beta-amyloid pathology in a case with dementia with Lewy bodies. p. 878–885, 2012, with permission from Elsevier.⁴⁷

and Alzheimer Disease Neuroimaging Initiative demonstrated that the NIA-AA criteria apply to most subjects with MCI in both the community and clinical trial settings; however, a sizeable proportion of subjects had conflicting biomarkers, which need to be investigated.²⁹ In this population, neurodegeneration on MRI increased the rate of progression to dementia in patients with MCI due to AD and appeared to be a key factor in predicting progression relative to A β deposition alone.

Molecular imaging studies with A β -binding ligands in preclinical AD indicate that approximately one-third of the population of cognitively normal individuals and 71% of patients with MCI in the community have high cortical A β loads. In cognitively normal individuals, high levels of A β deposition are associated with subtle cognitive deficits, cognitive decline, and a higher risk of cognitive impairments in the future. However, these relationships appear to be modified by the genetic markers,^{5,30} lifestyle activities,³¹ or cognitive reserve.³²

Molecular Imaging for the Differential Diagnosis of AD

The high sensitivity and specificity of PiB binding to fibrillar A β have been demonstrated in vitro,³³ in mouse models,³⁴ and in human tissue.³⁵ The newer [^{18}F] agents for A β PET have undergone a similar validation process^{36–40} and appear to show properties similar to those of PiB.^{41–45} The specificity of PiB to fibrillar A β is preserved even in patients with protein deposits associated with other neurodegenerative dementias such as α -synuclein in dementia with Lewy bodies (DLB) (Fig 3).^{46–49} However, there may be disagreements between the postmortem report and the PET findings because of the heterogeneity of A β deposits. For example, PiB labels both neuritic and diffuse plaques, though labeling of diffuse/amorphous plaques is less prominent than that of compact/cored plaques.^{35,50} Patients with dementia with Lewy bodies or Parkinson disease dementia, who typically have high loads of diffuse plaques, may have positive A β PET scan findings but would not be classified as having AD because of the absence of

neuritic plaques and a low Braak neurofibrillary tangle stage.^{46,47} Another example is cerebral amyloid angiopathy. PiB binds to vascular amyloid in patients with cerebral amyloid angiopathy, but not all patients with cerebral amyloid angiopathy have parenchymal A β deposits for the diagnosis of AD. Thus, while PiB is highly specific to A β , not all A β deposits may be considered for the pathologic diagnosis of AD.^{35,50} Furthermore, there appears to be a threshold for detection in which it may not be possible to detect low levels of fibrillar A β deposition.⁵¹ Nonetheless, the agreement between high A β load on PET and a pathologic diagnosis of AD in the clinical setting is high and is demonstrated in antemortem imaging and postmortem confirmation studies and case series.^{52–54} The sensitivity and specificity of amyloid PET tracers to the different

fibrillar A β deposits need further investigation.

One of the key applications of A β PET imaging in clinical practice is in the differential diagnosis of AD. The accuracy of A β PET in distinguishing AD and frontotemporal lobar degeneration is quite high,⁵⁵ with an overall classification accuracy of 97% in cases with histopathologic confirmation.⁵⁶ On the other hand, the 2 most common dementia pathologies after AD are vascular disease and Lewy body pathologies, which commonly are present with additional AD pathology. In these cases, the presence of an intermediate-to-high A β load may be insufficient to determine the predominant pathology contributing to the dementia syndrome. In keeping with the postmortem data, 25%–35% of patients with vascular dementia^{57,58} and 60%–80% of patients with DLB^{46,54,59–62} have high A β loads on PET. Thus high levels of amyloid load may be insufficient in distinguishing these dementia syndromes from AD, and a multitechnique imaging approach may be useful. We have shown that FDG-PET, A β PET, and structural MR imaging are complementary in distinguishing patients with AD and DLB⁵⁴ and may be useful in predicting the presence of AD pathology in patients with DLB (Fig 4).⁶³ Molecular imaging of the impaired nigrostriatal dopaminergic transmission in DLB with 2 β -carbomethoxy-3 β -(4-iodophenyl)-N-(3-fluoropropyl) nortropane with SPECT⁶⁴ or loss of monoaminergic terminal integrity with vesicular monoamine transporter type 2 radioligands may further detect the Lewy body-related pathologic features in cases with mixed dementia and may be complementary to A β PET.⁶⁵

The added diagnostic value of A β PET imaging in the differential diagnosis of dementia across different clinical settings has become a topic of significant interest with the availability of [^{18}F] agents for A β imaging.^{66–70} Although the added value of A β PET to clinical decision-making has not been established,^{66–69} how A β load is measured on PET scans (ie, visual evaluation versus various quantitative techniques) appears to make a difference in the value of this diagnostic technique in the clinical setting.⁶⁹

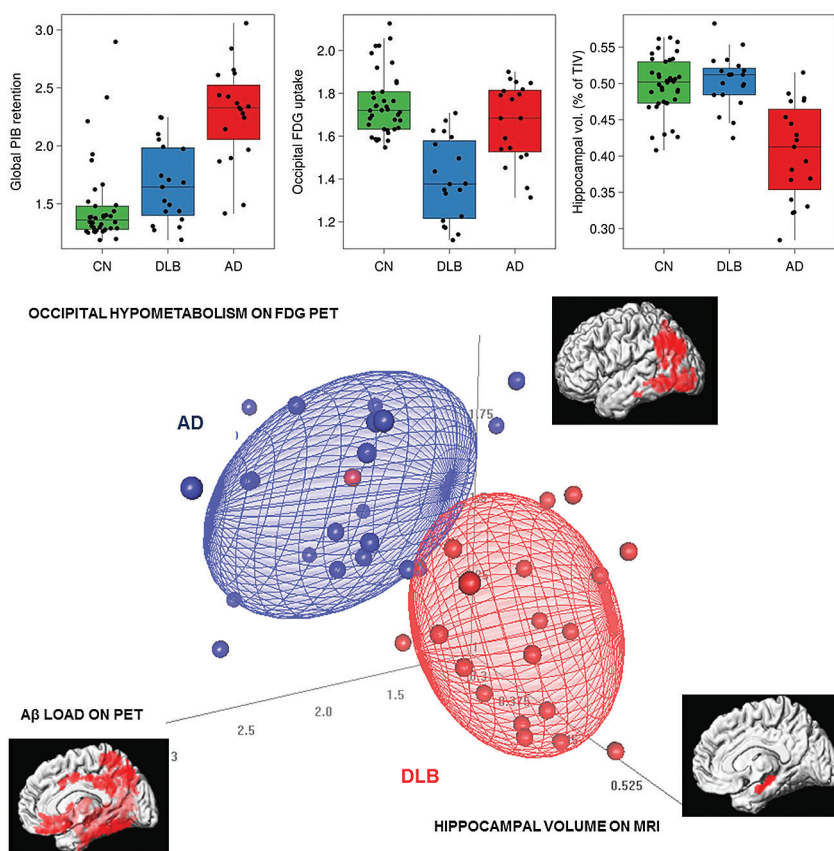


FIG 4. Multitechnique imaging markers in distinguishing Alzheimer disease and dementia with Lewy bodies. Regional FDG hypometabolism and PiB uptake on PET in patients with probable DLB ($n = 21$) are compared with those in control subjects ($n = 42$); and gray matter atrophy in patients with AD ($n = 21$) is compared with that in patients with DLB, displayed on surface-rendered brain images by using SPM (Wellcome Department of Imaging Neuroscience, London, UK) ($P < .05$; family-wise error corrected for multiple comparisons). Although occipital lobe hypometabolism, global cortical PiB retention, and hippocampal volumes (percentage of total intracranial volume) were overlapping among patients with probable DLB and AD as shown in box-plots in the top panel, a multitechnique imaging approach almost completely separated the patients with DLB and AD. Logistic regression modeling demonstrated that each imaging technique independently contributed to distinguishing the patients with AD and DLB with an area under the receiver operating characteristic curve of 0.98. Reprinted from *Neurobiology of Aging*, Vol. 33(9), Kantarci K, Lowe VJ, Boeve BF, et al. Multimodality imaging characteristics of dementia with Lewy bodies. p. 2091–2105, 2012, with permission from Elsevier.⁴⁵

Longitudinal Molecular Imaging for Tracking AD Pathology

Longitudinal imaging of the $A\beta$ load on PET provides evidence of the progression of $A\beta$ deposition in the preclinical-to-clinical AD spectrum. The hypothetical model proposed by Jack et al⁷¹ indicates that $A\beta$ deposition detected with molecular imaging and CSF biomarkers follows an accelerated course early in the disease process during the preclinical and MCI stages but slows down during the Alzheimer disease stage and reaches a plateau at very high levels. The findings of many longitudinal biomarker studies on $A\beta$ deposition agree with this model.^{72–81} Cognitively normal individuals who progress to MCI and patients with MCI who progress to AD appear to have the highest rates of $A\beta$ deposition,⁷⁹ correlating with cognitive decline early in the disease course.^{76,77} Furthermore, a higher baseline $A\beta$ load^{78,80} and the presence of $APOE \epsilon 4$ ⁷⁹ are associated with higher rates of $A\beta$ deposition. However, the association between higher baseline $A\beta$ load measured with the standardized uptake value ratio and a

higher rate of $A\beta$ deposition appear to dissipate at very high levels (roughly 2.0 standardized uptake value ratio). After this threshold, the relationship becomes an inverted U, gradually declining and reaching zero at the highest baseline $A\beta$ load levels (2.7 standardized uptake value ratio). The time estimated to start with positive findings on a PiB scan (1.5 standardized uptake value ratio) to the point of plateau is approximately 15 years, corresponding to a large therapeutic window for clinical trials.⁷³

Molecular Imaging in Clinical Trials for AD

In autosomal dominant AD, the age of symptom onset can be predicted. It is estimated that increased $A\beta$ deposition precedes clinical symptoms for approximately 15 years, providing a wide window for preventive therapies.^{82,83} The role of molecular imaging in clinical trials targeting the pathology captured with the molecular imaging agent can be 2-fold: 1) to determine who has the target pathology and enrichment of trials with this information; and 2) to determine whether a treatment is modifying the target pathology. Both of these applications of $A\beta$ imaging are being used in current clinical trials of amyloid-modifying therapies for both treatment and prevention of AD.^{84,85} Findings from the bapineuzumab phase 2 double-blind placebo-controlled, ascending-dose study indicate that lowering of cortical fibrillar $A\beta$ with bapineuzumab can be detected with PiB PET.⁸⁶ However, even though there were reductions in the $A\beta$ load, the bapineuzumab trials were halted due to lack of improvement in clinical and functional outcomes in patients with AD dementia. Similarly, it is expected that imaging of the τ pathology of AD^{87,88} especially with agents specific to the τ pathology that are currently being developed and tested,⁸⁹ will open avenues for development of new targets for prevention.

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