Alzheimer disease identification using amyloid imaging and reserve variables

Proof of concept

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ABSTRACT

Objective: Several factors may influence the relationship between Alzheimer disease (AD) lesions and the expression of dementia, including those related to brain and cognitive reserve. Other factors may confound the association between AD pathology and dementia. We tested whether factors thought to influence the association of AD pathology and dementia help to accurately identify dementia of the Alzheimer type (DAT) when considered together with amyloid imaging.

Methods: Participants with normal cognition ($n = 180$) and with DAT ($n = 25$), aged 50 years or older, took part in clinical, neurologic, and psychometric assessments. PET with the Pittsburgh compound B (PiB) tracer was used to measure brain amyloid, yielding a mean cortical binding potential (MCBP) reflecting PiB uptake. Logistic regression was used to generate receiver operating characteristic curves, and the areas under those curves (AUC), to compare the predictive accuracy of using MCBP alone vs MCBP together with other variables selected using a stepwise selection procedure to identify participants with DAT vs normal cognition.

Results: The AUC resulting from MCBP alone was 0.84 (95% confidence interval [CI] = 0.73–0.94; cross-validated AUC = 0.80, 95% CI = 0.68–0.92). The AUC for the predictive equation generated by a stepwise model including education, normalized whole brain volume, physical health rating, gender, and use of medications that may interfere with cognition was 0.94 (95% CI = 0.90–0.98; cross-validated AUC = 0.91, 95% CI = 0.85–0.96), an improvement ($p = 0.025$) over that yielded using MCBP alone.

Conclusion: Results suggest that factors reported to influence associations between AD pathology and dementia can improve the predictive accuracy of amyloid imaging for the identification of symptomatic AD. *Neurology*® 2010;75:42–48

GLOSSARY

A β = amyloid- β ; **AD** = Alzheimer disease; **AUC** = area under receiver operating characteristic curve; **BP** = binding potential; **CDR** = Clinical Dementia Rating; **CI** = confidence interval; **DAT** = dementia of the Alzheimer type; **DV** = distribution volume; **MCBP** = mean cortical binding potential; **nWBV** = normalized whole brain volume; **OR** = odds ratio; **PiB** = Pittsburgh compound B; **ROC** = receiver operating characteristic curve; **ROI** = region of interest.

Autopsy data indicate a discrepancy between the burden of Alzheimer disease (AD) lesions (amyloid plaques and neurofibrillary tangles) in the brain and the expression of dementia symptoms during life, such that some individuals with high levels of plaques and tangles at autopsy did not have dementia proximate to death.^{1–3} Amyloid imaging, which allows in vivo observation of brain amyloid- β (A β),⁴ has been proposed as a diagnostic tool that can be used for early and accurate identification of this hallmark of AD pathology.^{5,6} However, studies using amyloid imaging continue to indicate incongruence between the presence of brain A β and the clinical expression of AD, with some people having an elevated amyloid burden but no dementia or cognitive impairment.^{7,8}

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Several factors have been identified that may influence the relationship between AD lesions and the expression of dementia, and may therefore help explain the discrepancies between brain A β and clinical symptomatology. The brain reserve and cognitive reserve hypotheses propose that certain anatomic features (brain reserve) and cognitive processing approaches (cognitive reserve) provide a buffer against brain damage due to AD, allowing one to tolerate a greater burden of AD pathology without manifesting dementia symptoms.^{1,9,10} Greater brain reserve is thought to result from greater numbers and health of neurons in the cortex, and has been assessed using measures such as head circumference,¹¹ whole brain volume,¹² and intracranial volume.¹² Destruction of or damage to brain tissue, such as that resulting from stroke, would decrease available brain reserve. Major factors that are thought to reflect or influence cognitive reserve (i.e., efficient use of brain networks or the ability to recruit alternate brain networks or cognitive strategies) include educational attainment^{11,13-16} and occupational experience.^{13,17}

Other factors have been found to be associated with dementia or cognitive impairment even in the absence of AD, and may therefore confound the association between brain A β and dementia symptoms. These include non-AD dementing disorders,¹⁸ depression,¹⁸⁻²² particular medical conditions,^{18,21-23} and certain medications.^{21,24,25}

We tested whether factors thought to influence the association of AD pathology and dementia help to accurately identify dementia of the Alzheimer type (DAT) when considered together with amyloid imaging.

METHODS A retrospective study was conducted using previously collected data from volunteers enrolled in longitudinal studies of aging and memory at the Washington University Alzheimer's Disease Research Center. Detailed information about the recruitment and assessment methods are available.²⁶ Briefly, individuals with normal cognition and dementia are recruited from the greater St. Louis, MO, area for participation. Exclusion criteria include the presence of a medical or psychiatric illness (e.g., renal failure requiring dialysis, use of insulin, or depression requiring electroconvulsive therapy) that could interfere with longitudinal follow-up or adversely impact cognition. At baseline and at all annual assessments, participants and their collateral sources take part in separate semi-structured interviews conducted by an experienced clinician. Participants also com-

plete a general physical and neurologic examination, the Mini-Mental State Examination,²⁷ the Geriatric Depression Scale,²⁸ psychometric testing, and MRI. Since April 2004, participants also undergo PET imaging with Pittsburgh compound B (PiB) for measurement of brain A β .

Standard protocol approvals, registrations, and patient consents. Study protocols were approved by the Washington University Medical Center Human Subjects Committee, and written informed consent was obtained from all participants.

Inclusion criteria. Data were taken from the most recent PET/PiB imaging session between April 15, 2004, and December 8, 2008, and the clinical assessment closest to the scan, for participants aged 50 years or older with a primary diagnosis of normal cognition or DAT (figure 1). In order to compare predictive models for the same individuals, participants also were required to have nonmissing data for all candidate variables of interest.

Clinical assessment. The Clinical Dementia Rating²⁹ (CDR) for each participant was determined by combining information from the participant and collateral source interviews. Possible intraindividual cognitive decline is assessed in 6 domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care). The global CDR score is derived from ratings of each domain in accordance with a standard scoring algorithm: CDR 0 = normal cognition, CDR 0.5 = very mild dementia, CDR 1 = mild dementia, CDR 2 = moderate dementia, and CDR 3 = severe dementia.

The diagnosis of DAT is made in accordance with standard criteria³⁰ based on evidence that the participant has experienced gradual onset and progression of memory and other cognitive problems that represent a change from a previous higher level of functioning, and that interferes with usual activities at home and in the community. The CDR 0.5 individuals in this study all had a diagnosis of DAT based on these criteria. In addition to the primary diagnoses, additional diagnoses can be recorded to document any other medical conditions that may affect cognition (e.g., depression).

Alzheimer's Disease Research Center clinicians complete extensive training, including observations of clinical assessments and CDR scoring.³¹ Clinician trainees also review a series of teaching and reliability videotapes of participants across the full spectrum of CDR stages and with DAT and non-DAT diagnoses. Certification in the CDR is achieved with an 80% agreement or better by the trainee with the gold standard videotapes. Clinicians are blind to the imaging results for each participant.

Imaging. Three-dimensional regions of interest (ROIs) are drawn on each participants' MRI after being coregistered to the PET scan. Regional time-activity curves from the ROIs are compared to a cerebellum reference region using a graphical analysis approach to calculate a distribution volume (DV).⁷ A binding potential (BP) value proportional to the number of binding sites for each ROI is calculated using the equation $BP = DV - 1$. The mean cortical binding potential (MCP) is obtained by taking the mean of the BPs from brain regions known to have high uptake among participants with DAT: the prefrontal cortex, gyrus rectus, lateral temporal cortex, and precuneus.⁷ Imaging staff are blinded to the participant's CDR and clinical diagnosis. The person (M.A.M.) directing the processing of the PET scan to generate the MCP value has over 25 years of experience in PET image analysis. He developed and published the original and standard approaches for estimating the number of binding sites from PET scan using radiolabeled ligands in the

Figure 1 Flow diagram for participant inclusion

CDR = Clinical Dementia Rating; DAT = dementia of the Alzheimer type; GDS = Geriatric Depression Scale; nWBV = normalized whole brain volume; PiB = Pittsburgh Compound B. *Participation was tied to recruitment goals for PET PiB imaging studies.

brain. No adverse events have occurred as a result of PET PiB imaging at Washington University.

Statistical analyses. Logistic regression was first used to generate a receiver operating curve (ROC) and the area under the ROC curve (AUC), using MCBP as the sole predictor of a DAT diagnosis. A second logistic regression analysis was conducted by entering MCBP into the model first, and then using the stepwise selection procedure to identify additional demographic, brain reserve, cognitive reserve, and other variables linked to cognitive impairment that improved model fit. Candidate variables available for stepwise selection were demographic factors (age at PET/PiB scan, gender, race [minority vs nonminority], the collateral source's rating of the participant's general physical health [excellent, good, fair, or poor]), *APOE4* genotype, cognitive reserve factors (years of education, the occupation ranking of the Hollingshead Index of Social Position³²), brain reserve factors (normalized whole brain volume [nWBV³³], history of stroke or TIA), depression (score on the Geriatric Depression Scale, a concomitant diagnosis of depression or bereavement), the presence of another medical condition that may interfere with cognition (e.g., vitamin B12 deficiency, traumatic brain injury), or use of a medication that may interfere with cognition (e.g., benzodiazepines/sedatives, specific antidepressants [e.g., tricyclics], anticholinergics). A significance level of 0.15 was used for entering and for exiting effects. The difference between the AUCs resulting from the 2 logistic models was tested statistically. Leave-one-out estimation was used to cross-validate the ROCs and their AUCs. Analyses were conducted using SAS version 9.1 (SAS Institute, Inc., Cary, NC).

RESULTS Mean (SD) Mini-Mental State Examination scores were 29.1 (1.3) for participants with normal cognition ($n = 180$, 87.8%) and 24.6 (3.9) for

participants with DAT (table 1). Previously, we reported that individuals with DAT diagnoses typically have MCBP values ≥ 0.18 .⁷ We found 34/180 CDR 0, 11/17 CDR 0.5, 7/7 CDR 1, and 1/1 CDR 2 participants had MCBP values above that level. Mean (SD) MCBP values were 0.11 (0.23) and 0.57 (0.39) for participants with normal cognition and DAT, respectively.

When tested alone, higher MCBP values increased the likelihood of DAT diagnosis (odds ratio [OR] 54.86, 95% confidence interval [CI] 14.19–212.11, $p < 0.0001$). The resulting AUC was 0.84 (95% CI 0.73–0.94; cross-validated AUC 0.80, 95% CI 0.68–0.92). Table 2 shows the ORs for variables that met entry criterion and were retained in the stepwise logistic regression model. As shown in table 2, worse physical health ratings were associated with an increased likelihood of having a DAT diagnosis, and more years of education and larger nWBVs were associated with a decreased likelihood of DAT. Two other variables that met criteria for model entry ($p = 0.15$), and aided in prediction, did not meet the traditional criterion for significance ($p = 0.05$). Male sex ($p = 0.09$) was related to a higher likelihood of DAT, and surprisingly, use of a medication that may interfere with cognition was associated with a decreased likelihood of DAT ($p = 0.09$). The stepwise model generated an AUC of 0.94 (95% CI 0.90–0.98; cross-validated AUC

Table 1 Demographics

	Values
Time between PET/PiB scan and clinical assessment, y, mean (SD)	0.5 (0.4)
Age at PET/PiB scan, y, mean (SD)	69.5 (10.0)
Women, n (%)	136 (66.3)
Minority race, n (%)	24 (11.7)
Education, y, mean (SD)	15.5 (2.9)
Occupation group, n (%)	
Higher executives	59 (28.8)
Business managers	63 (30.7)
Administrative personnel	22 (10.7)
Clerical and sales	38 (18.5)
Skilled and semiskilled employees	10 (4.9)
Unskilled employees	13 (6.3)
General physical health rating, n (%)	
Excellent	85 (41.5)
Good	102 (49.8)
Mild or moderate impairment	18 (8.8)
Clinical Dementia Rating, n (%)	
0	180 (87.8)
0.5	17 (8.3)
1	7 (3.4)
2	1 (0.5)
Medical condition that may interfere with cognition, n (%)	12 (5.9)
Medication that may interfere with cognition, n (%)	71 (34.6)
Depression or bereavement diagnosis, n (%)	20 (9.8)
Geriatric Depression Scale, mean (SD) ^a	0.8 (1.2)
Mean cortical binding potential, mean (SD)	0.16 (0.29)
Normalized whole brain volume, cm ³ , mean (SD)	0.77 (0.04)

Abbreviation: PiB = Pittsburgh compound B.

^a Scores range from 0 to 15, with higher scores indicating more depressive symptoms.

0.91, 95% CI 0.85–0.96), an improvement ($p = 0.025$) over that yielded using MCBP alone. Figure 2 shows the improvement in the AUC as each variable is added to the predictive model.

DISCUSSION While elevated MCBP is strongly associated with AD, we also found high MCBP levels among 19% of our cognitively normal older adults. Our results suggest that DAT in the presence of elevated amyloid is also a function of particular characteristics and attributes of the individual.

When adjusted for MCBP, the strongest predictors of DAT included education and nWBV. Greater educational attainment was associated with a lower likelihood of DAT, lending further support to the hypothesis that cognitive reserve factors are impor-

Table 2 Stepwise logistic regression results predicting likelihood of a diagnosis of dementia of the Alzheimer type

Effect	OR (95% CI)	p Value
Mean cortical binding potential	100.83 (16.93–600.40)	<0.0001
Education, y	0.69 (0.54–0.88)	0.003
Physical health rating		0.005
Excellent (reference)	1.00 (—)	
Good	2.69 (0.66–10.91)	
Mild or moderate impairment	30.47 (3.79–244.82)	
Normalized whole brain volume	0.15 (0.03–0.95)	0.044
Medication that may interfere with cognition	0.30 (0.07–1.22)	0.092
Male sex	3.00 (0.85–10.41)	0.090

Abbreviations: CI = confidence interval; OR = odds ratio.

tant mediators of the effect of AD pathology on cognition.^{9,10} Likewise, larger nWBVs predicted a lower likelihood of DAT and may reflect greater neuronal reserve,¹ absence of neuronal death due to AD, or both.

Worse ratings of physical health also predicted DAT, consistent with reports that individuals with AD show reductions in physical function and physical activity.³⁴ Further, physical fitness may have a neuroprotective effect,³⁵ while physical frailty has been found to predict incident AD.³⁶ Surprisingly, less frequent use of medications with the potential to affect cognition was observed for participants with a DAT diagnosis, although not reaching the traditional criterion for significance ($p = 0.09$). We do not currently understand this finding, which may be spurious. Speculatively, this effect may be a consequence of recommendations regarding use of these medications in dementia provided by clinician investigators. Advice that such medications may adversely impact cognition and the recommendation to review indications for the drugs with the primary care provider would have been made during feedback sessions.

Interestingly, age and *APOE4* genotype, long known as the strongest risk factors for AD, did not enter the stepwise models as significant predictors of DAT. The first variable to enter the model, and the one with the lowest p value, was MCBP. Because age and *APOE* genotype interact to increase the frequency of cerebral $A\beta$ deposition in cognitively normal older adults,³⁷ it is possible that older age and *APOE4* may be risk factors for AD primarily via their association with increasing brain $A\beta$ levels. Aging is associated with decreasing brain volume even among

Figure 2 Receiver operating characteristic (ROC) curves for all model building steps in the stepwise analysis

Model step 1 is the ROC curve with mean cortical binding potential (MCBP) as the sole predictor of a dementia of the Alzheimer type diagnosis. Steps 2–6 show the area under the ROC curve with the addition of each additional significant predictor using the stepwise selection method (2 = education, 3 = physical health rating, 4 = normalized whole brain volume, 5 = gender, 6 = use of a medication that may interfere with cognition). No predictors were removed from the model after meeting the criterion for model entry. AUC = area under receiver operating characteristic curve.

cognitively normal adults,³³ and age is correlated with nWBV in our sample ($r = -0.79$, $p < 0.0001$). Therefore, an alternative explanation for the failure of age to enter the models is that because age and nWBV are so closely associated, once one of these variables has entered the model, the other adds little additional predictive power.

The failure of age and *APOE* genotype to enter the models may instead be due to the modest number of participants with DAT, which is a limitation of our study. Replication with larger samples may identify additional, or alternate, factors that help to predict DAT when considered with amyloid imaging results. Therefore, these results should be considered preliminary. Although we included a clinical history of stroke or TIA as a candidate variable, an additional limitation is that we were unable to examine MRI evidence of vascular disease, as this is not routinely measured in our cohort.

We used PET/PiB imaging to measure brain A β . Due to its approximately 20-minute half-life, the use of PiB is restricted to research sites with the ability to manufacture the radiotracer themselves.³⁸ Researchers are working to develop and validate radiotracers with longer half-lives, such as fluoride-18 agents.³⁸

Given these limitations, our results confirm earlier work indicating that the appearance of dementia

is a combined result of AD pathology and other factors reflecting individual differences across people.^{9,10} Indeed, adding only 2 variables (education and general health) increased the accuracy of an amyloid imaging–based model to identify DAT almost 10%. Multivariable models are currently in use in other areas of medicine to enhance diagnostic accuracy³⁹ and predict treatment success.⁴⁰ Although much work remains before such models are ready for use, our results suggest that the predictive value of AD biomarkers for the determination of DAT rather than simply the presence of AD pathology may benefit from consideration of individual differences in demographic characteristics, cognitive reserve, and brain reserve.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Catherine M. Roe.

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