What does fluorodeoxyglucose PET imaging add to a clinical diagnosis of dementia?

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ABSTRACT

Background: Few studies have compared the accuracy of [^{18}F]fluorodeoxyglucose (FDG) PET to the accuracy of clinical and pathologic diagnosis in dementia patients.

Methods: Forty-four individuals with dementia, cognitive impairment, or normal cognitive function underwent clinical initial evaluation (IE) and PET scanning and were followed up for approximately 4 years until a final evaluation (FE) and 5 years until death and autopsy. Clinical, pathologic, and imaging diagnoses were categorized as Alzheimer disease (AD) or not AD.

Results: Sensitivity of the IE for the pathologic diagnosis of AD was 0.76, and specificity was 0.58; PET had values of 0.84 and 0.74, and FE had values of 0.88 and 0.63. Positive predictive values for IE, PET, and FE were 0.70, 0.81, and 0.76. Negative predictive values were 0.65, 0.78, and 0.80. The diagnosis of AD was associated with a 70% probability of detecting AD pathology; with a positive PET scan this increased to 84%, and with a negative PET scan this decreased to 31%. A diagnosis of not AD at IE was associated with a 35% probability of AD pathology, increasing to 70% with a positive PET scan.

Conclusions: As a diagnostic tool, PET is superior to a baseline clinical evaluation and similar to an evaluation performed 4 years later. Although the addition of [^{18}F]fluorodeoxyglucose PET to a clinical diagnosis provides useful information that can affect the likelihood of detecting Alzheimer disease pathology, the value of this technique in the current clinical environment with limited therapeutic options is likely to be modest. ***Neurology*® 2007;69:871–877**

Although PET with the glucose metabolic tracer [^{18}F]fluorodeoxyglucose (FDG) has been widely applied to the study of dementia for more than two decades, its use is still controversial in clinical management, and it has not received wide acceptance in practice.[1] Nevertheless, many studies report that Alzheimer disease (AD) is associated with diminished metabolism in the parietal and temporal cortex, posterior cingulate cortex, and precuneus, a pattern that is often distinct from normal aging and other dementias.[2-4] Most existing studies compare FDG-PET to a clinical diagnosis, which may be inaccurate and therefore not an ideal gold standard. In addition, the use of clinical diagnosis as a criterion does not permit a comparison of the relative accuracy of FDG-PET diagnosis and clinical diagnosis to neuropathologic diagnosis, nor does it allow an assessment of how much additional information, over and above that obtained with a clinical diagnosis, the imaging technique can provide.

Only two studies have enrolled subjects to specifically evaluate the clinical utility of FDG-PET in comparison with pathology.[5,6] From 1994 to 2002, we evaluated and followed a group of subjects who were studied with FDG-PET and had serial clinical evaluations and a neuropathologic examination at death. Here we report the diagnostic accuracy of FDG-PET in comparison with clinical evaluations in these subjects relative to a postmortem pathologic diagnosis.

Supplemental data at www.neurology.org

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METHODS Subject selection and diagnosis. The subjects of this report were those individuals who had at least one clinical evaluation, a pathologic examination, and an FDG-PET scan. First, a list of all subjects with neuropathologic examinations who were clinically evaluated at the University of California Davis AD Center was generated; this database was cross-tabulated with a database of all subjects who underwent FDG-PET on a modern multislice PET scanner. All subjects had an initial clinical evaluation in relatively close temporal proximity to the FDG-PET scan. After this initial evaluation (IE) and FDG-PET study, subjects were followed for varying periods, with repeat clinical evaluations. The majority of subjects in this report thus had two clinical examinations: the first in conjunction with the PET scan, and the final evaluation (FE) in relatively close proximity to death and autopsy. Three subjects died after the IE before a second evaluation was performed.

Subjects were seen by a multidisciplinary team composed of, at minimum, a neurologist, neuropsychologist, and nurse, and sometimes including a geriatrician, psychiatrist, or social worker for all clinical evaluations. Varying degrees of neuropsychological testing were performed, depending on clinical indications. Cognitive instruments included the Mini-Mental State Examination (MMSE),[7] Clinical Dementia Rating scale,[8] and standard neuropsychological tests of episodic memory, executive functions, attention, expressive language, and visuoconstructive ability. After this evaluation, subjects underwent an MRI scan that was used to rule out structural lesions or to define the presence and extent of cerebrovascular disease.

At each clinical evaluation, a diagnosis was established at a multidisciplinary conference after review of all clinical data. Initially, subjects were assigned a syndrome category of normal, demented, or cognitively impaired but not demented (CIND). Subjects with CIND had either a single circumscribed cognitive deficit or multiple deficits that were not severe enough to impair function and meet dementia criteria.[9] Individuals with diagnoses of dementia were assigned a specific etiology. Consistent standard criteria were used for the diagnosis of AD[10] and vascular dementia[11] during the entire period, whereas diagnostic criteria for dementia with Lewy bodies (DLB)[12,13] and frontotemporal lobar degeneration (FTLD)[14,15] varied somewhat during the study as these criteria evolved. Mixed dementia was diagnosed when AD and vascular dementia were deemed equally likely causes of the cognitive decline.

All subjects were evaluated at approximately annual intervals and seen by a neurologist, nurse, and neuropsychologist, and repeated neuropsychological testing was performed as long as subjects were deemed testable, usually when the MMSE score was 15 or greater. Any diagnostic change prompted a multidisciplinary conference review of all clinical information.

PET imaging and image evaluation. FDG-PET imaging was performed on either a Siemens-CTI ECAT EXACT or ECAT EXACT HR tomograph in two-dimensional mode after the injection of 5 to 10 mCi of FDG. Images were acquired for 30 or 40 minutes, approximately 20 to 30 minutes after tracer injection, and all images were corrected for attenuation with transmission scans obtained with a rotating external positron source. Images were reconstructed using standard two-dimensional filtered backprojection. Images were not available at the time of clinical diagnostic evaluation and were not used in any way in the diagnostic process.

Images were evaluated by two raters (W.J. and C.D.) blind to clinical and pathologic diagnoses. Both raters had extensive experience reading FDG-PET scans in research settings and had previously participated in studies using visual rating scales to assess images in dementia patients. Images were displayed on video display terminals on which orientation (axial, coronal, sagittal) and color scale could be manipulated. Raters were asked to make a judgment about whether the image reflected the presence of AD or not. Images consistent with AD were agreed upon a priori to show bilateral temporal or parietal hypometabolism or both, highly asymmetric temporoparietal hypometabolism, or posterior cingulate hypometabolism. Frontal hypometabolism was thought to be consistent with a diagnosis of AD if it was accompanied by more severe temporoparietal hypometabolism. After a session in which the raters independently evaluated images, the raters reviewed images on which they disagreed and came to a consensus diagnosis. The results of these readings thus represent the consensus imaging diagnosis for all cases.

Neuropathologic examination. Although exact autopsy protocols varied somewhat during the study period, in general the entire brain was fixed in formalin (often after the dissection of specific areas for freezing) and processed for examination. Extensive tissue blocks were sampled, exceeding recommendations by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD).[16] Sections were routinely stained with hematoxylin and eosin, Congo red, and Bielschowsky silver stains, and in general were examined with antibodies to A-beta, tau, ubiquitin, alpha-synuclein, and glial fibrillary acidic protein. During the study period, a single neuropathologist was responsible for all diagnoses, and the CERAD diagnostic criteria for AD were used for all cases, with final diagnoses defined as definite, probable, or possible according to these criteria.[16] Subjects autopsied in later years also received a final diagnosis according to the National Institute on Aging (NIA)–Reagan Institute criteria.[17]

Data analysis. The aim of this study was to evaluate the potential ability of both clinical and imaging diagnoses to detect AD. Thus, all diagnoses were dichotomized into "AD" or "not AD." Clinically probable and possible AD were considered equivalent. Clinical diagnoses of mixed dementia (AD with vascular dementia) and DLB were coded as "AD" because clinicians thought that AD pathology was likely contributing in these cases. Similarly, pathologic diagnoses were considered as dichotomous, with CERAD diagnoses of definite and probable AD considered as "AD," and CERAD possible AD considered as "not AD." Pathologic diagnoses of both mixed dementia (AD plus cerebrovascular disease) and DLB (AD plus Lewy bodies) were considered as "AD" only if the neuropathologic criteria for CERAD probable or definite AD were met as well. This classification scheme thus resulted in dichotomous clinical and FDG-PET diagnoses that could be compared with the dichotomous pathologic diagnoses. Sensitivity, specificity, and positive and negative predictive values were calculated for IE, FE, and PET diagnoses with respect to final pathologic diagnosis.

An additional group of analyses using logistic regression models was performed to define the incremental diagnostic

Table 1 Subject characteristics	
Men/women	29/15
Mean age at IE	75 (11)
Mean education	14 (3)
MMSE score	23 (5.7)
Diagnoses at IE: AD	
AD	20
MIX	4
DLB	3
Diagnoses at IE: non-AD	
Normal	9
CIND	4
Vascular dementia	1
FTLD	1
Unknown	2

Values are mean (SD) and, for diagnoses and sex, number of subjects in each category.
IE = initial evaluation; MMSE = Mini-Mental State Examination; AD = Alzheimer disease; MIX = mixed dementia; DLB = dementia with Lewy bodies; CIND = cognitively impaired but not demented; FTLD = frontotemporal lobar degeneration.

value of PET imaging over and above the clinical evaluation. An initial logistic regression evaluated the relationship between the clinical diagnosis (AD or not AD) and pathologic diagnosis (AD or not AD). Subsequently, a second analysis evaluated the predictive performance of the clinical diagnosis at IE combined with PET diagnosis in comparison with pathology.

RESULTS A total of 45 subjects had autopsies, clinical evaluations, and PET scans. One subject met inclusion criteria but had a PET scan that was deemed uninterpretable because of motion artifact, leaving a group of 44 subjects in whom all data were available. The composition of the group is shown in table 1. Most subjects were diagnosed with AD clinically (2/20 were possible AD, and the remainder were probable AD). Combined with the 4 subjects with mixed dementia and 3 with DLB, 27 subjects were thought to have AD pathology on clinical grounds. The remaining non-AD diagnoses included 9 cognitively normal subjects, 2 of whom presented for dementia evaluations but were deemed normal and 7 of whom were recruited from the community as control subjects. All 4 individuals diagnosed with CIND presented for clinical evaluation of cognitive decline, but a dementia diagnosis was not established.

The time between the IE and FE averaged 4.1 years (SD 2.7), during which time a number of clinical diagnoses were revised. One subject moved from an AD diagnosis (AD) to a non-AD diagnosis (FTLD), and 3 subjects moved from non-AD diagnoses (normal, CIND, unknown) to AD diagnoses (AD).

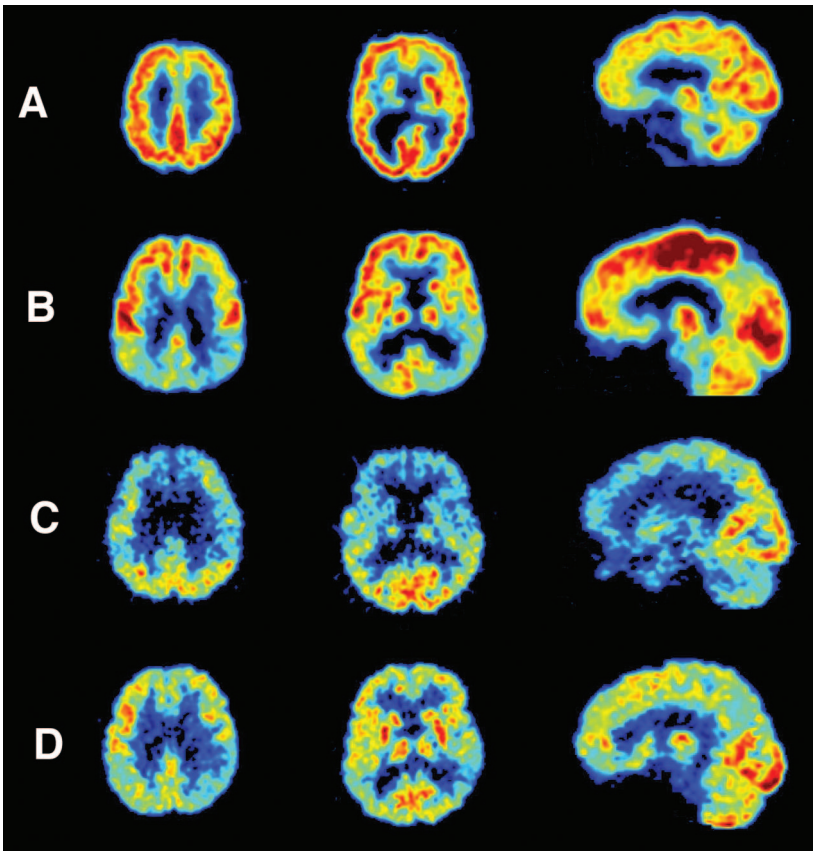
Pathologic examination was performed an average of 4.9 years (SD 2.6) after IE and 0.74 years (SD 0.8) after FE. Nineteen cases met criteria for AD without other pathologic processes (16 definite, 3 probable). In general, CERAD criteria for definite AD corresponded to NIA–Reagan high likelihood, probable AD to intermediate likelihood, and possible AD to low likelihood, although 16 cases did not have NIA–Reagan ratings. Four cases met CERAD criteria for possible AD without other pathology and were categorized as "not AD." There were two cases with DLB that also met CERAD criteria for possible AD and were categorized as "not AD." Eight cases had mixed Alzheimer and cerebrovascular pathology, of which 6 were categorized as "AD" (1 of these 6 met criteria for CERAD possible AD but NIA–Reagan intermediate likelihood). Thus, a total of 25 cases were characterized as AD, and 19 were non-AD. Additional non-AD diagnoses included normal brain (2), FTLD (2), cerebrovascular disease without AD pathology (5), and other (2 cases, one unidentified leukoencephalopathy and the other alcoholic encephalopathy with Korsakoff syndrome).

PET imaging was performed an average of 1.3 years after IE (SD 2.0), but this time interval had a skewed distribution such that the median time between the IE and PET was 0.3 years. The time between PET scanning and death was more normally distributed and averaged 3.6 years (SD 2.3, median 3.0). The two raters reviewing images independently had only modest agreement on the individual ratings before the consensus ratings, agreeing on 73% of cases, with a kappa statistic of 0.43. Figure 1 shows examples of PET images.

Table 2 shows the sensitivity, specificity, and positive and negative predictive values for the IE, FE, and PET compared with pathology. The ability of clinical diagnosis to predict pathology improved from the first to last evaluation for all measures, with sensitivity superior to specificity at both time points. PET showed sensitivity slightly superior to IE and somewhat below FE, whereas specificity for PET was greater in comparison with both clinical evaluations. Positive and negative predictive values for PET were superior to clinical IE and comparable to clinical FE.

Because diagnostic performance may be affected by disease severity, we evaluated this relationship in two ways. We selected all subjects with MMSE score > 23, producing a subgroup of 25 subjects with a mean MMSE score of 27.2. In

Figure 1 Representative PET scans for Alzheimer disease (AD) and non-AD cases



(A) 87-year-old woman recruited as a control subject, classified as cognitively normal at both initial evaluation (IE) and final evaluation (FE), PET scan read as not AD (normal), died 4.4 years after IE, brain pathologically classified as normal. (B) 71-year-old man presented with cognitive symptoms, diagnosed as AD at both evaluations, PET scan read as AD, died 2 years after IE, pathologically classified as AD (Consortium to Establish a Registry for Alzheimer's Disease [CERAD] definite, National Institute on Aging [NIA]–Reagan high likelihood). (C) 62-year-old man presented with cognitive symptoms, diagnosed as frontotemporal lobar degeneration (FTLD) at both evaluations, PET scan read as not AD (FTLD), died 6.6 years after IE, pathologically classified as not AD (FTLD). (D) 54-year-old man presented with cognitive symptoms but classified as cognitively normal at IE, PET scan read as AD, diagnosed as AD at FE (8 years after IE), died 9 years after IE, pathologically classified as AD (CERAD definite).

these individuals, sensitivity, specificity, and positive and negative predictive values of FDG-PET were considerably higher than IE and somewhat higher than FE (table E-1 on the *Neurology* Web site at www.neurology.org). In addition, we evaluated the course of the individuals who were deemed normal at IE. PET scans of 3 of theses 9 individuals were interpreted as positive for AD. By FE, one of the subjects who had presented with cognitive symptoms developed a clinical diagnosis of AD that was confirmed as definite AD at autopsy. This individual's PET was read as showing AD (figure 1). The second subject developed CIND at FE and had CERAD possible AD (NIA–Reagan low likelihood) at autopsy. The third individual with an AD-pattern PET scan remained cognitively normal at FE but had pathology indicative of both vascular disease and CERAD possible AD (in this case, NIA–Reagan intermediate likelihood, qualifying for an AD pathologic diagnosis). One additional subject developed CIND at FE and had CERAD possible AD (NIA–Reagan low likelihood) at autopsy, but in this case the PET was read as not AD. Two additional subjects with negative PET scans remained cognitively normal, one met criteria for CERAD probable AD and one met criteria for CERAD possible AD, and 2 subjects remained cognitively normal and had a normal brain at autopsy. The remaining subject, who had presented with cognitive complaints, had a normal PET, was judged normal at FE, and at autopsy had cerebrovascular disease. Sensitivity and specificity for PET in detecting AD in these normal subjects were 0.67 and 0.83.

Because PET scanning was performed months after the IE, we investigated whether this delay was related to the improved diagnostic accuracy of PET by performing a subanalysis on subjects with an interval between PET and IE of <6 months. In this group of 31 subjects with a mean MMSE score of 22.6, the mean and median intervals between IE and PET were approximately 3 months. Results for sensitivity, specificity, and positive and negative predictive values were virtually identical to the group as a whole (table E-2).

Figure 2 shows the results of the logistic regression models. In a model comparing only clinical diagnosis at IE to pathology, the probability of AD pathology is 70% if the diagnosis is AD and 35% if the diagnosis is not AD. Clinical diagnosis was a significant predictor of pathologic classification in this model ($p = 0.03$). In a multivariate logistic regression including both clinical diagnosis at IE and PET diagnosis as predictors of pathology, PET diagnosis was a predictor ($p = 0.002$), whereas clinical diagnosis was not ($p = 0.29$). In this model, a clinical diagnosis of AD was associated with a probability of AD pathology of 84% with a positive PET scan, and 31% with a negative PET scan. When the clinical diagnosis at IE was not AD, a positive PET scan increased the probability of AD pathology from 35% to 70%, and a negative PET scan decreased the probability to 17%. Clinical diagnosis alone at FE was a predictor of pathology ($p = 0.001$), and in this case the probability of AD pathology was 76% if the diagnosis was AD and 20% if the diagnosis was not AD (data not shown).

DISCUSSION This study adds to the limited available data on the relationship between FDG-PET imaging and neuropathology in dementia

Table 2 Sensitivity, specificity, and positive and negative predictive values of clinical diagnosis at initial and final evaluations and FDG-PET scan in comparison with pathologic diagnosis

	Clinical IE	FDG-PET	Clinical FE
Sensitivity	0.76	0.84	0.88
Specificity	0.58	0.74	0.63
Positive predictive value	0.70	0.81	0.76
Negative predictive value	0.65	0.78	0.80

IE = initial evaluation; FDG = [^{18}F]fluorodeoxyglucose; FE = final evaluation.

patients. We were able to compare the accuracy of PET to clinical diagnosis performed in the same subjects as well as to compare both the initial clinical evaluation and PET scanning with a later follow-up diagnosis. This design demonstrated that PET was more sensitive than the initial clinical diagnosis, but in fact somewhat less sensitive than the later clinical diagnosis. Specificity was substantially superior for PET compared with both IE and the FE. Both positive and negative predictive values were higher for PET than for IE, and PET was comparable in these metrics to FE, performed 4 years later. Thus, diagnostic sensitivity and specificity available with PET scanning near the time of initial diagnosis is similar to longitudinal clinical diagnosis over a number of years. A diagnosis of AD at IE, associated with a positive PET scan, is therefore slightly more likely to be associated with AD pathology than a diagnosis of AD at FE. Similarly, a diagnosis of not AD at baseline associated with a negative PET scan is similar in the prediction of pathology to a diagnosis of not AD at the FE. Thus, from a diagnostic perspective, obtaining a PET scan at IE improves the accuracy of the diagnosis by an amount roughly equivalent to the clinical information gained over several years of follow-up. Nevertheless, these findings should be tempered by our small sample size and the low interrater reliability in our PET readings, as well as by the limited therapeutic options that are currently available to clinicians treating AD.

The addition of PET to clinical diagnosis at IE had a substantial effect on the likelihood of finding AD pathology at postmortem, and was particularly important when PET disagreed with the clinical diagnosis. A positive PET scan increased the likelihood of AD pathology by 14% if the clinical diagnosis was AD, but by 35% if the clinical diagnosis was not AD. Conversely, a negative PET scan decreased the diagnosis by 18% if the clinical diagnosis was not AD, but by 39% if the diagnosis was AD. In both situations when PET disagreed with the clinical diagnosis, the correct pathologic diagnosis was in fact more likely to be congruent with PET than with the diagnosis at IE.

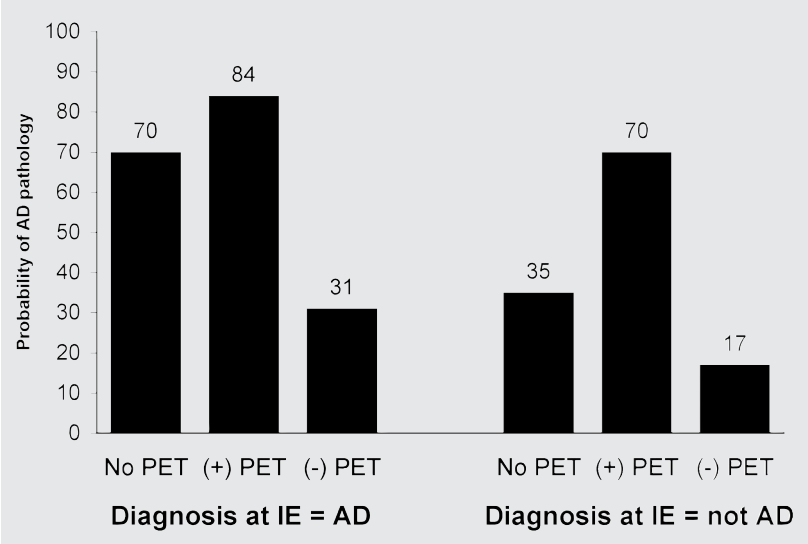
The data reported here agree with the two largest previously reported studies in demonstrating that PET sensitivity is superior to specificity.[5,6] In addition, calculation of likelihood ratios indicates that our results are similar to the two previous studies, with a positive likelihood ratio of 3.2 compared with 3.5[6] and 2.7[5] and negative likelihood ratios of 0.21 in our study and 0.08 and 0.17 in the two other studies. These results are consistent with a modest effect of PET information on the pretest likelihood. In addition, although our sample size is relatively small, it is larger than one of the previous reported studies and likely more representative of patients presenting with dementia. Whereas the majority of pathologic diagnoses were AD, 43% were non-AD.

The accuracy of clinical diagnosis in this series is consistent with previously reported studies,[1] although values for sensitivity and specificity vary widely (from 47% to 100% for both measures). Average values across 13 studies show sensitivity of 81% and specificity of 70%,[1] which is closer to our results at FE than at IE. Given these results, it seems unlikely that the value of PET in addition to the value of clinical diagnosis derives from exceptionally poor clinical accuracy in this cohort.

Few studies have directly studied the added value of imaging in conjunction with clinical evaluation in dementia patients. A previous report using SPECT in a manner similar to that reported here found that that a positive SPECT scan increased the likelihood of finding AD pathology from 84% on clinical diagnosis alone to 92%—a small but perhaps clinically useful effect.[18] A recent PET study classified subjects according to whether they were likely to progress and contrasted the clinical prediction of progression with the FDG-PET prediction of progression.[19] The clinical prediction of subsequent course had a sensitivity of 77% and specificity of 76%, whereas the sensitivity of PET was 95% and specificity was 79%. In the single study prospectively comparing clinical and imaging diagnoses with pathology, FDG-PET generally showed higher accuracy than clinical diagnosis, particularly by increasing sensitivity at the expense of specificity relative to the clinical diagnosis.[5]

Several features of this study differ from previous reports, in some ways strengthening our find-

Figure 2 Probability of Alzheimer disease (AD) pathology given different evaluation results



Leftmost three bars show results when a clinical diagnosis at the initial evaluation (IE) was AD without information from PET (No PET), when a PET was interpreted as positive for AD [(+) PET], and when PET was interpreted as negative for AD [(−) PET]. Rightmost three bars indicate the same conditions when the diagnosis at IE was not AD.

ings and in others limiting them. First, although the study included patients and controls from a university dementia clinic, these individuals were an average of 10 years older than those reported in the two previous PET series and were pathologically complex with a number of mixed dementia diagnoses and comorbid pathologies. Although our strategy of simplifying diagnoses to AD or not AD on pathologic grounds is a limitation, this is nevertheless a reasonable approach based on the considerable literature indicating the specificity of PET findings for AD. Indeed, the ability to detect AD pathology with PET even in the presence of comorbid cerebral infarction strengthens our results. Although occipital hypometabolism has been suggested as diagnostic of DLB[20,21] and frontotemporal hypometabolism for FTLD,[22,23] our sample did not contain adequate numbers of these different etiologies to independently evaluate diagnostic accuracy in these cases. Another limitation of our study is the delay between IE and PET examination, which could have improved the diagnostic performance of PET because of disease progression during this interval. However, based on our subanalysis and the fact that 70% of subjects were studied within 6 months of the IE, this seems an unlikely explanation. Finally, the procedures used for both clinical and imaging diagnosis in this study are unlikely to reflect standard clinical practice. An in-depth multidisciplinary team approach to clinical diagnosis, and the use of two experienced raters with a consensus imaging diagnosis may have maximized diagnostic accuracy of both clinical evaluation and PET scanning. Interestingly, the interrater reliability of image interpretation was not especially high, suggesting that diagnostic accuracy will not be independent of the rater in routine clinical settings.

Forcing clinical diagnoses into the dichotomous categories of "AD" and "not AD" could also be seen as a limitation, although in clinical practice this is often required and may become increasingly important as more effective therapies for AD become available. For example, a diagnosis of CIND, especially of the amnestic variety, could be considered equivalent to a diagnosis of AD. It is therefore worth noting that of our CIND cases, two ultimately met pathologic criteria for AD (one probable and one definite), but two did not (one had mixed cerebrovascular disease and possible AD, and one had only cerebrovascular disease). Including these subjects as clinical diagnoses of "AD" would have increased the sensitivity of diagnosis at IE to 0.84 at the expense of specificity (0.47).

The examination of subjects with mild dementia and cognitively normal subjects adds an interesting dimension to this report. The fact that two of the normal individuals presented with cognitive symptoms also adds clinical relevance. In these normal subjects, as well as in the subgroup with very mild dementia, sensitivity and specificity of PET were both reasonably high. These results are in keeping with other reports suggesting that PET may detect abnormalities in cognitively normal individuals who are destined to decline or dement,[24,25] as well as in individuals with very mild dementia and those with mild cognitive impairment.[2,26]

These results add to the small but growing literature indicating that FDG-PET can play a role in dementia diagnosis. The existing studies are strikingly similar in supporting a general theme that FDG-PET produces results comparable if not superior to a clinical diagnosis. Although we do not suggest that an FDG-PET study should supplant a careful clinical examination, PET findings consistent with AD support a clinical diagnosis of AD, and findings inconsistent with AD should prompt a thoughtful reevaluation.

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