Amyloid vs FDG-PET in the differential diagnosis of AD and FTLD

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ABSTRACT

Objective: To compare the diagnostic performance of PET with the amyloid ligand Pittsburgh compound B (PiB-PET) to fluorodeoxyglucose (FDG-PET) in discriminating between Alzheimer disease (AD) and frontotemporal lobar degeneration (FTLD).

Methods: Patients meeting clinical criteria for AD (n = 62) and FTLD (n = 45) underwent PiB and FDG-PET. PiB scans were classified as positive or negative by 2 visual raters blinded to clinical diagnosis, and using a quantitative threshold derived from controls (n = 25). FDG scans were visually rated as consistent with AD or FTLD, and quantitatively classified based on the region of lowest metabolism relative to controls.

Results: PiB visual reads had a higher sensitivity for AD (89.5% average between raters) than FDG visual reads (77.5%) with similar specificity (PiB 83%, FDG 84%). When scans were classified quantitatively, PiB had higher sensitivity (89% vs 73%) while FDG had higher specificity (83% vs 98%). On receiver operating characteristic analysis, areas under the curve for PiB (0.888) and FDG (0.910) were similar. Interrater agreement was higher for PiB (κ = 0.96) than FDG (κ = 0.72), as was agreement between visual and quantitative classification (PiB κ = 0.88–0.92; FDG κ = 0.64–0.68). In patients with known histopathology, overall classification accuracy (2 visual and 1 quantitative classification per patient) was 97% for PiB (n = 12 patients) and 87% for FDG (n = 10).

Conclusions: PiB and FDG showed similar accuracy in discriminating AD and FTLD. PiB was more sensitive when interpreted qualitatively or quantitatively. FDG was more specific, but only when scans were classified quantitatively. PiB slightly outperformed FDG in patients with known histopathology. ***Neurology*® 2011;77:2034–2042**

GLOSSARY

Aβ = β-amyloid; **AD** = Alzheimer disease; **CERAD** = Consortium to Establish a Registry for Alzheimer's Disease; **CI** = confidence interval; **DVR** = distribution volume ratio; **FDG** = fluorodeoxyglucose; **FTLD** = frontotemporal lobar degeneration; **NC** = normal control; **PiB** = Pittsburgh compound B; **ROC** = receiver operator characteristic; **ROI** = region of interest; **TDP** = TAR DNA-binding protein 43.

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Differentiating Alzheimer disease (AD) and frontotemporal lobar degeneration (FTLD) has implications for prognosis and symptomatic treatment,[1,2] and is critical for the efforts to develop disease-specific therapies. Making an accurate diagnosis during life can be challenging given overlapping clinical features.[3,4] MRI or fluorodeoxyglucose PET (FDG-PET) can improve diagnostic accuracy by demonstrating distinct topographic patterns of atrophy or hypometabolism (temporoparietal predominant in AD; frontal and anterior temporal involvement in FTLD),[5,6] but anatomic overlap between the diseases is increasingly apparent.[5,7] Consequently, many patients with pathologically confirmed FTLD are diagnosed with AD during

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Supplemental data at www.neurology.org

Supplemental Data

From the Memory & Aging Center and Departments of Neurology (G.D.R., H.J.R., A.A., A.K., M.E.G., J.Y.J., L.T.G., M.L.G.-T., W.W.S., B.L.M., W.J.J.), Epidemiology and Biostatistics (J.K.), and Pathology (E.J.H., S.J.D.), University of California San Francisco, San Francisco; Helen Wills Neuroscience Institute (G.D.R., A.A., A.J.F., N.A., E.C.M., W.J.J.), University of California Berkeley, Berkeley; Lawrence Berkeley National Laboratory (G.D.R., A.J.F., E.C.M., J.P.O., M.J., W.J.J.), Berkeley, CA; and Center for Neurodegenerative Research (J.Q.T.), University of Pennsylvania, Philadelphia.

Study funding: This work was supported by the National Institute on Aging grants K23-AG031861, R01-AG027859, P01-AG1972403, and P50-AG023501; State of California Department of Health Services Alzheimer's Disease Research Center of California grant 04-33516; Alzheimer's Association grants NIRG-07-59422 and ZEN-08-87090; John Douglas French Alzheimer's Foundation; and the Consortium for Frontotemporal Dementia Research.

Disclosure: Author disclosures are provided at the end of the article.

life, and conversely 10%–40% of patients clinically diagnosed with FTLD are found to have AD postmortem.[8–10]

PET with β-amyloid (Aβ)–specific ligands such as Pittsburgh compound B (PiB)[11] could help distinguish AD and FTLD, since Aβ plaques are a hallmark of AD but are not part of the FTLD pathologic spectrum. Furthermore, the differential diagnosis of AD and FTLD usually arises in patients with early-onset dementia, in whom amyloid plaques related to age rather than disease state are less common. Small series have demonstrated the potential of amyloid imaging to differentiate AD and FTLD,[12–14] but diagnostic utility has not been evaluated in a large cohort or compared to currently available clinical tools. We evaluated the diagnostic performance of PiB-PET in differentiating AD and FTLD, and compared it to the performance of FDG-PET, which is approved by the US Centers for Medicare and Medicaid Services for this indication.

METHODS

Study population. The study was designed in accordance with the Standards for Reporting Diagnostic Accuracy criteria.[15] Patients were recruited from AD and FTLD research cohorts followed at the University of California San Francisco Memory and Aging Center. All patients underwent an evaluation by experienced clinicians that included a neurologic examination, neuropsychometric tests, and structural MRI. Clinical diagnosis was assigned at a multidisciplinary conference which included MRI review, but clinicians were blinded to PET results. To be eligible for this study, patients were required to meet research criteria for AD[16] or the FTLD syndromes behavioral variant frontotemporal dementia, semantic dementia, or progressive nonfluent aphasia.[17] Patients with posterior cortical atrophy and logopenic aphasia, visuospatial and language-predominant syndromes associated with AD pathology[18] were included in the AD group to represent the full clinical spectrum of early-onset AD.[19] Exclusion criteria included clinical features consistent with an alternative primary neurologic disorder (e.g., significant cerebrovascular disease, epilepsy, tumors, dementia with Lewy bodies, prion disease), major medical illness, and premorbid psychiatric disease. Cognitively normal imaging controls (NC) were selected from a convenience sample recruited from the community.[20] NC were functioning independently and performed within normal limits on neuropsychometric testing. The 25 youngest individuals in the NC cohort with available PiB and FDG data were selected (table 1).

Standard protocol approvals, registrations, and patient consents. Written informed consent was obtained from all patients (or guardians of patients) participating in the study. The study was approved by the University of California (San Francisco and Berkeley) and Lawrence Berkeley National Laboratory institutional review boards for human research.

PET acquisition and analysis. Subjects underwent [^{11}C]PiB and [^{18}F]FDG-PET on a Siemens ECAT EXACT HR scanner at Lawrence Berkeley National Laboratory as previously described.[12] FDG frames for each subject were summed and normalized to mean activity in the pons. For PiB, voxel-wise distribution volume ratios (DVRs) were calculated using Logan graphical analysis (cerebellar reference).[12] See appendix e-1 on the *Neurology*® Web site at www.neurology.org for details.

Table 1 Subject characteristics and group-level PET averages[a]

Syndromic diagnosis	AD (n = 62)[b]	FTLD (n = 45)[c]	NC (n = 25)	p	Post hoc
Age at PET, y	65.0 ± 9.9	64.8 ± 6.7	69.8 ± 3.5	0.03	AD and FTLD vs NC, $p < 0.05$
Years from first symptom	5.2 ± 2.8	5.5 ± 2.8		0.56	
Male: female	35: 27	24: 21	8: 17	0.11	
Education, y	16.3 ± 2.8	14.9 ± 2.9	17.4 ± 1.8	0.001	FTLD vs NC, $p < 0.005$; AD vs FTLD, $p < 0.05$
MMSE	22.3 ± 5.7	22.0 ± 8.1	29.5 ± 0.7	<0.005	AD and FTLD vs NC, $p < 0.005$
CDR	0.9 ± 0.5	1.1 ± 0.8		0.08	
CDR-SB	4.9 ± 3.1	6.0 ± 4.3		0.16	
*APOE*4 (0, 1, 2)	20, 15, 8	32, 8, 2	13, 12, 0	0.004	FTLD vs NC and AD, $p < 0.05$
PiB index	1.61 ± 0.27	1.13 ± 0.27	1.19 ± 0.17[d]	<0.005	AD vs NC and FTLD, $p < 0.005$
FDG-AD, *Z*	−1.67 ± 1.40	−0.52 ± 1.33	0.00 ± 1.00	<0.005	AD vs NC and FTLD, $p < 0.005$
FDG-FTLD-frontal, *Z*	−0.77 ± 1.39	−1.56 ± 1.74	0.00 ± 1.00	<0.005	FTLD vs NC, $p < 0.005$; FTLD vs AD, $p < 0.05$
FDG-FTLD-temporal, *Z*	−0.77 ± 1.39	−1.28 ± 1.49	0.00 ± 1.00	0.001	FTLD vs NC, $p < 0.005$
FDG, *Z* difference	0.61 ± 1.01	−1.45 ± 1.15	−0.20 ± 0.41	<0.005	AD vs FTLD and NC, $p < 0.005$; FTLD vs NC, $p < 0.005$

Abbreviations: AD = Alzheimer disease; CDR-SB = Clinical Dementia Rating sum of boxes; FDG = fluorodeoxyglucose; FTLD = frontotemporal lobar degeneration; MMSE = Mini-Mental State Examination; NC = normal control; PiB = Pittsburgh compound B.

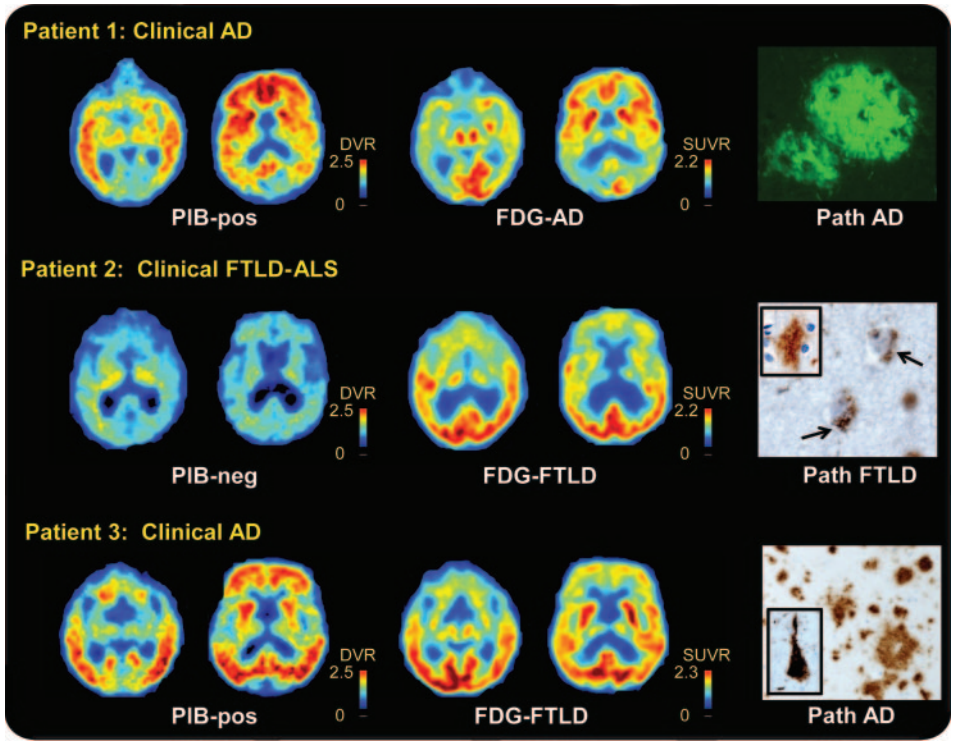
[a] Data are mean ± SD. Missing data: CDR: AD 4, FTLD 1; PiB index: AD 2, FTLD 2; FDG: AD 3, FTLD 4; *APOE*: AD 19, FTLD 3.

[b] AD (memory), n = 38; posterior cortical atrophy, n = 13; logopenic aphasia, n = 11.

[c] Behavioral-variant frontotemporal dementia, n = 21; semantic dementia, n = 13; progressive nonfluent aphasia, n = 11.

[d] After iterative outlier elimination (see Methods), mean PiB index in NC was 1.11 ± 0.045.

Figure 1 Pittsburgh compound B (PiB), fluorodeoxyglucose (FDG), and histopathology in selected patients



Images are displayed in neurologic orientation and in NIH color scale as viewed by the visual raters. Patient 1 (clinical Alzheimer disease [AD]) showed diffuse cortical and striatal PiB binding (PiB-positive by consensus) and temporoparietal-predominant hypometabolism on FDG (FDG-AD by consensus). Autopsy was consistent with high-likelihood AD: amyloid plaques in temporal cortex are illustrated on staining with thioflavin-S, a dye that is structurally related to PiB. Patient 2 (clinical frontotemporal lobar degeneration [FTLD]–amyotrophic lateral sclerosis [ALS]) was PiB-negative by consensus, with FDG demonstrating frontal-predominant hypometabolism (consensus FDG-FTLD). Pathologic diagnosis was FTLD-TDP with motor neuron disease: characteristic TDP-43 cytoplasmic inclusions are demonstrated in anterior cingulate neurons by immunohistochemistry (arrows). Early Aβ pathology in the form of diffuse plaques was also found (insert: Aβ immunohistochemistry in occipital cortex). Patient 3 (clinical AD) was PiB-positive by consensus, but FDG showed frontal hypometabolism suggestive of FTLD (FDG-FTLD by consensus). Autopsy revealed Consortium to Establish a Registry for Alzheimer's Disease frequent neuritic plaques (shown: Aβ immunohistochemistry in middle frontal gyrus) and Braak stage 6 neurofibrillary pathology (insert: tau immunohistochemistry in posterior cingulate cortex) consistent with high-likelihood AD.

Visual ratings. Patient PET scans were visually rated by 2 experienced investigators (W.J.J. and H.J.R.) blinded to clinical data. PiB DVR images and FDG pons-normalized images were presented in the NIH color scale and could be windowed and viewed in 3 planes at the rater's discretion. PiB scans were rated as "PiB-positive" if tracer binding was deemed greater in cortical gray matter than in white matter, and as "PiB-negative" if only nonspecific white matter binding was observed. FDG images were rated as "AD" if hypometabolism was judged to be greatest in temporoparietal cortex, and as "FTLD" if hypometabolism was deemed most severe in frontal or anterior temporal cortex.[6] Representative scans are shown in figure 1. Both raters were given a priori rating criteria, but a formal training session was not performed.

Quantitative classification. PET values were extracted from predefined regions of interest (ROIs; see appendix e-1). PiB index (mean DVR in frontal, lateral parietal, precuneus, lateral temporal, and cingulate cortex), a global measure of binding, was used to define scan positivity.[20] A quantitative threshold for PiB positivity (PiB index $\geq$1.20) was empirically defined as 2 standard deviations above the mean for controls after first excluding controls with high PiB binding using iterative outlier elimination[21] (see appendix e-1).

For FDG, regional values were extracted from an AD ROI (lateral and medial temporoparietal cortex) and 2 FTLD ROIs: FTLD-frontal (frontal cortex anterior to precentral gyrus) and FTLD-temporal (temporal pole and amygdala). Two ROIs were deemed necessary for FTLD to capture cases with relatively focal frontal or anterior temporal hypometabolism.[22] ROIs in every patient were assigned a Z score based on regional uptake in the NC group. Patient FDG scans were classified based on the ROI with the lowest Z score (e.g., classified as AD if Z score was lower in AD than in both FTLD ROIs). The difference in Z scores between the AD ROI and the lowest FTLD ROI for each patient was calculated as Z difference = Z (FTLD-lowest) − Z (AD).

Genetics and neuropathology. *APOE* genotyping was performed on patients and NC (table 1). Tests for FTLD-associated mutations in progranulin (n = 33), microtubule-associated protein tau (n = 20), and TDP-43 (n = 20), and AD-associated mutations in presenilin-1 (n = 1) and presenilin-2 (n = 2), were performed on a subset of patients.

Table 2 PET results and diagnostic parameters[a]

	PiB			FDG		
PET classifications	Rater 1	Rater 2	Quantitative	Rater 1	Rater 2	Quantitative
Clinical AD (n = 62)	56 pos/6 neg	55 pos/7 neg	54 pos/7 neg	44 AD/15 FTLD	47 AD/12 FTLD	43 AD/16 FTLD
Clinical FTLD (n = 45)	8 pos/36 neg	7 pos/37 neg	7 pos/35 neg	6 AD/35 FTLD	7 AD/34 FTLD	1 AD/40 FTLD
Sensitivity, %	90 (80–96)	89 (78–95)	89 (78–95)	75 (62–85)	80 (67–89)	73 (60–84)
Specificity, %	82 (67–92)	84 (70–93)	83 (69–93)	85 (71–94)	83 (68–93)	98 (87–100)
Positive predictive value, %	88 (77–94)	89 (78–95)	89 (78–95)	88 (76–95)	87 (75–95)	98 (88–100)
Negative predictive value, %	86 (71–95)	84 (70–93)	83 (69–93)	70 (55–82)	74 (59–86)	71 (58–83)
Likelihood ratio-positive	4.97 (2.80–10.63)	5.58 (2.96–12.42)	5.31 (2.87–12.06)	5.10 (2.54–13.09)	4.67 (2.45–10.14)	29.88 (11.61–40.00)
Likelihood ratio-negative	0.12 (0.04–0.24)	0.13 (0.06–0.26)	0.14 (0.06–0.27)	0.30 (0.18–0.46)	0.25 (0.13–0.40)	0.28 (0.17–0.41)

Abbreviations: AD = Alzheimer disease; FDG = fluorodeoxyglucose; FTLD = frontotemporal lobar degeneration; NC = normal control; PiB = Pittsburgh compound B.
[a] PiB scans were classified as PiB-positive (pos) or negative (neg), while FDG scans were read as classified as consistent with AD or FTLD. In parentheses are 95% confidence intervals. Missing data: PiB: one scan (FTLD patient) aborted and unclassifiable; 3 scans (1 AD, 2 FTLD) excluded from quantification due to motion artifact. FDG: 7 patients (3 AD, 4 FTLD) did not undergo scan.

Fourteen patients who participated in the study have died, and brain autopsies are available for 11 (mean time from PET to death 2.2 ± 1.3 years). Ten autopsies were performed at UCSF and one at the University of Pennsylvania. The autopsy protocols have been described previously (see appendix e-1).[10] Published criteria were applied for the pathologic diagnosis of AD[23] and FTLD.[24]

Statistical analysis. Group differences in continuous variables were examined using analysis of variance with post hoc Tukey correction or Student *t* test. Group differences in dichotomous variables were compared using χ^2 or Fisher exact tests. Agreement in classifying scans was measured using Cohen kappa statistic (κ). Sensitivity, specificity, positive and negative predictive values were estimated by the appropriate observed proportion, and 95% confidence intervals were generated based on the assumption that they follow a binomial distribution. Positive and negative likelihood ratios were derived from the estimates of sensitivity and specificity. Confidence intervals for κ and positive/negative likelihood ratios were generated using the adjusted bootstrap percentile method with 10,000 resamples. Sensitivity and specificity of PiB and FDG were compared using χ^2. Inter-rater agreement for PiB and FDG was compared by testing for a nonzero difference between κ(PiB) [κ(FDG)] using the bootstrap method given above. Statistical analysis was implemented in PASW 18.0 (SPSS Inc.) and *R* (http://www.r-project.org/).

RESULTS

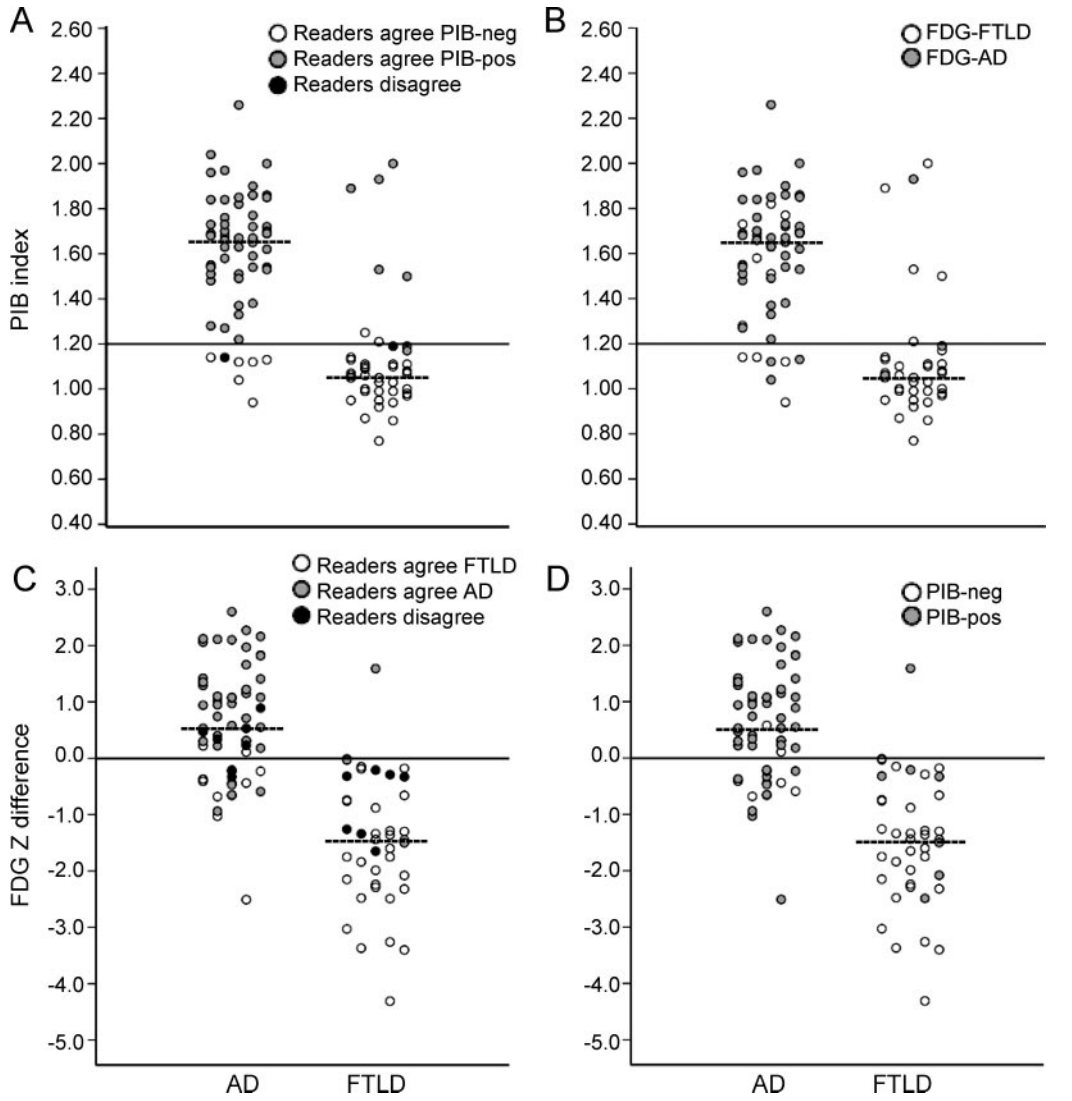
Patient characteristics. Subjects were recruited consecutively between April 2005 and June 2010. Data from subsets of patients have been reported in previous series.[12,22,25] Patients with AD and patients with FTLD were well matched for demographic and disease measures (table 1). One patient with clinical FTLD and ALS was found to have a mutation in TDP-43 (A90V) that has been linked to FTLD with motor neuron disease.[26] No other known mutations were identified in tested patients.

A flow chart demonstrating missing and excluded data are presented in figure e-1. One PiB scan was aborted due to patient discomfort after 40 minutes (before washout of unbound tracer) and was thus excluded from further analysis. PiB DVR images could not be produced for 3 additional scans due to patient motion. These scans were excluded from quantitative classification, and visual ratings were performed on summed images from late time points ($t \geq 40$ minutes) divided by mean activity in the cerebellar reference region.[11] Seven patients did not undergo FDG due to technical problems or subject preference. There were no adverse events associated with the study.

PiB and FDG vs clinical diagnosis. At a group level, PiB Index was higher in AD than in NC and FTLD (table 1), and was similar in FTLD and NC ($p = 0.61$). Patients with AD had lower FDG uptake than NC and FTLD in the AD ROI, and patients with FTLD had lower FDG than NC in FTLD-frontal and FTLD-temporal, and lower FDG than patients with AD in FTLD-frontal (table 1).

PET results by clinical diagnosis are shown in table 2 and figure 2 (see table e-1 and figure e-2 for results by AD and FTLD subsyndromes). PiB showed higher sensitivity (89%–90%) for AD than FDG (73%–80%). This difference was significant for Rater 1 classifications ($p = 0.04$) and nearly significant for quantitative classifications ($p = 0.051$). PiB and FDG visual ratings had similar specificity (PiB 82%–84%, FDG 83%–85%), but quantitative classification greatly improved the specificity of FDG (98%) compared to PiB (83%, $p = 0.07$). PiB had higher negative predictive values and lower negative likelihood ratios than FDG. Visual ratings of PiB and FDG showed similar positive predictive values and positive likelihood ratios, while on quantitative classification positive predictive value and positive likelihood ratio were higher for FDG (table 2).

Figure 2 Pittsburgh compound B (PiB) and fluorodeoxyglucose (FDG) scatterplots by clinical diagnosis



PiB index (measure of cortical PiB binding) is displayed by (A) visual read or (B) FDG majority classification (best of 3 between 2 visual ratings and quantitative classification). FDG *Z* difference (difference in *Z* scores between lowest frontotemporal lobar degeneration (FTLD) and Alzheimer disease (AD) regions of interest) is displayed by (C) visual read or (D) majority PiB classification (best of 3 between 2 visual ratings and quantitative classification). Horizontal solid lines represent quantitative thresholds for PiB positivity (PiB index ≥ 1.20) or FDG-AD classification (FDG *Z* difference >0); hatched lines represent group median values.

PiB showed higher interrater agreement (κ = 0.96, 95% confidence interval [CI] 0.86–1.00) than FDG (κ = 0.72, 0.56–0.84; $p < 0.001$). Agreement between visual ratings and quantitative classification was very high for PiB (κ = 0.88 and 0.92 for the 2 raters), with disagreements occurring at the threshold of positivity (figure 2A). Agreement between visual ratings and quantitative FDG classifications was more modest (κ = 0.64 and 0.68, figure 2C).

When scans were classified by majority between 2 visual ratings and quantitative classification, PiB and FDG agreed in classifying 83% of patients (PiB-positive and FDG-AD or PiB-negative and FDG-FTLD), κ = 0.64 (95% CI 0.47–0.78, figure 2, B and D).

Receiver operator characteristic analysis. Receiver operator characteristic (ROC) analyses were performed to compare the discriminatory power of PiB index and FDG *Z* difference in our dataset (figure e-3). The ROC-derived thresholds that maximized overall classification accuracy for PiB index (1.215) and FDG *Z* difference (0.05) were nearly identical to our prespecified thresholds (1.20, 0.00) and thus yielded similar sensitivity (PiB 89%, FDG 73%) and specificity (PiB 86%, FDG 98%) to classification using a priori thresholds (table 2). Areas under the curve for PiB index (0.888, 95% CI 0.809–0.966) and FDG *Z* difference (0.910, 0.851–0.971) were similar.

Table 3 Patients with known histopathology[a]

Clinical diagnosis	Age at PET, y	Sex	*APOE*	PiB visual reads	PiB Index	FDG visual reads	FDG *Z* diff	PET to death, y	Primary autopsy diagnosis	AD pathology, CERAD, Braak
AD (memory)	71.3	M	ε4/ε3	Pos/Pos	1.72	AD/AD	2.09	3.3	High-likelihood AD[c]	Frequent, 5/6
AD (memory)	58.1	M	ε4/ε4	Pos/Pos	1.22	AD/AD	1.19	3.8	High-likelihood AD	Frequent, 6
AD (memory)	89.9	M	ε3/ε3	Pos/Pos	1.77	FTLD/FTLD[b]	−2.51[b]	0.7	High-likelihood AD[d]	Frequent, 6
FTLD (bvFTD)	58.1	M	ε3/ε3	Neg/Neg	0.99	FTLD/AD[b]	−1.34	0.8	Pick disease	Absent, 0
FTLD (SD)	58.3	F	ε3/ε4	Neg/Neg	0.87	FTLD/FTLD	−3.22	2.6	Pick disease	Moderate, 1
FTLD (bvFTD-ALS)	58.4	M	ε4/ε4	Neg/Neg	0.99	FTLD/FTLD	−1.32	0.9	FTLD-TDP/MND	Sparse, 2
FTLD (bvFTD-ALS)	64.2	M	ε3/ε3	Neg/Neg	1.03	FTLD/FTLD	−1.75	2.0	FTLD-TDP/MND	Absent, 2
FTLD (bvFTD)	74.1	F	ε3/ε3	Neg/Neg	1.11	NA	NA	1.1	FTLD-TDP[e]	Absent, 2
FTLD (bvFTD)	68.3	M	ε3/ε3	Neg/Neg	1.25[b]	NA	NA	2.1	FTLD-TDP[f]	Sparse, NA
FTLD (SD)	81.0	M	ε3/ε3	Neg/Neg	1.05	FTLD/FTLD	−1.34	4.7	FTLD-TDP[g]	Absent, 1
FTLD (SD)	69.3	M	ε4/ε4	Neg/Neg	1.13	FTLD/FTLD	−0.01	2.6	FTLD-TDP[h]	Frequent, 3
FTLD (bvFTD-ALS)	71.1	M	ε3/ε3	Neg/Neg	0.97	FTLD/FTLD	−3.4	NA	FTLD-TDP (mutation)	NA

Abbreviations: AD = Alzheimer disease; ALS = amyotrophic lateral sclerosis; bvFTD = behavioral-variant frontotemporal dementia; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; FDG = fluorodeoxyglucose; FTLD = frontotemporal lobar degeneration; MND = pathologically confirmed motor neuron disease; NA = not available; NC = normal control; PiB = Pittsburgh compound B; TDP = TAR DNA-binding protein 43.

[a] The primary contributing pathology in the opinion of the neuropathologist is listed in the table. The degree of AD pathology found in every case is rated using CERAD score for neuritic plaques and Braak stage for neurofibrillary pathology. Additional secondary pathologies noted in subscript.

[b] PET results that were incongruent with the primary autopsy diagnosis.

[c] Low-density limbic Lewy bodies.

[d] Moderate subcortical ischemic vascular disease; low-density Lewy bodies in brainstem and amygdala.

[e] Moderate to frequent tau-positive, Bielschowsky-negative cytoplasmic inclusions and neuropil threads in hippocampus and entorhinal cortex.

[f] Neurofibrillary tangles in limbic areas, inferior temporal gyrus, and precentral gyrus. Astrocytic tau-positive inclusions found in the same regions, but in smaller numbers. This pattern does not fit existing criteria for a specific tauopathy and precludes Braak staging.

[g] Early-stage progressive supranuclear palsy.

[h] Moderate amyloid angiopathy; argyrophilic grain disease.

PET results in patients with known histopathology. Clinical and pathologic diagnoses were congruent in all 12 patients with known histopathology (11 autopsies and 1 mutation carrier, table 3). PiB visual reads correctly predicted the primary histopathology in every case. One patient with primary FTLD with TAR DNA-binding protein 43 positive inclusions (FTLD-TDP), read as PiB-negative by both visual raters, had a PiB index (1.25) just above the positive threshold (1.20). This patient had early diffuse plaques (rated as sparse by Consortium to Establish a Registry for Alzheimer's Disease [CERAD] criteria[23]). However, 3 other patients with primary FTLD and comorbid plaques (ranging from CERAD sparse to frequent) were PiB-negative visually and quantitatively. FDG scans (available in 10/12 patients) misclassified 1 patient with pathologically proven AD on both visual ratings and on quantitative assessment (patient 3 in figure 1). One patient with autopsy-confirmed FTLD (Pick disease) was misclassified on 1/2 FDG visual reads. Overall classification accuracy (combining 2 sets of visual reads and quantitative classification for each patient) was 97% (35/36) for PiB and 87% (26/30) for FDG.

DISCUSSION This study examined the diagnostic utility of PiB-PET in discriminating between AD and FTLD in a large sample of clinically well-characterized patients, and compared it to the diagnostic performance of FDG-PET, which has an established role in differentiating the 2 diseases.[6] We found that amyloid imaging was sensitive and specific in differentiating AD from FTLD, thus fulfilling an important criterion for an AD biomarker.[27] FDG-PET is already recognized by US health authorities as useful in this clinical scenario, yet our study suggests that PiB performs at least as well, and has the additional advantages of higher sensitivity and better accuracy and precision of qualitative reads. Furthermore, PiB slightly outperformed FDG in patients with known histopathology. These findings support a role for amyloid imaging in the differential diagnosis of AD and FTLD.

Diagnosing the cause of dementia during life currently relies on correlations between clinical syndromes, topographic patterns of neurodegeneration, and underlying histopathology. The limitations of this approach are increasingly evident, as clinicopathologic studies demonstrate clinical and anatomic overlap between diseases.[4,5,7,9] While PiB directly measures molecular pathology, neuroimaging techniques such as MRI and FDG-PET measure the secondary effects of disease on brain structure and

function, and may ultimately fail to predict the underlying histopathology when neurodegeneration does not conform to characteristic topographic patterns. For example, 20%–27% of patients with clinically diagnosed AD in our study were judged to have an FTLD-like metabolic pattern, consistent with previous reports that frontal involvement is common in early-age-at-onset AD.[28] The majority of these patients were PiB-positive (figure 2D), including 1 patient with pathologically confirmed AD (figure 1, patient 3).

Visual ratings of PiB scans had a higher sensitivity for AD than visual ratings of FDG, with similar specificity. Based on our a priori quantitative thresholds, PiB had higher sensitivity and negative predictive value and lower negative likelihood ratio, while FDG showed higher specificity, positive predictive value, and positive likelihood ratio (table 2). On ROC analysis, PiB and FDG were found to have similar discriminatory power (nearly identical AUC) but different diagnostic strengths, with PiB showing higher sensitivity and FDG higher specificity at thresholds that optimized overall classification accuracy. These findings suggest a complementary diagnostic role for PiB and FDG. When evaluating a patient with early-onset dementia, the clinician's first imperative is to "rule out" AD, since symptomatic treatments are currently available and novel therapies for AD (many of which target Aβ) are in advanced clinical trials. This could be achieved with PiB with high sensitivity. If the clinical assessment and PiB are at odds, FDG could add value as the more specific diagnostic test, particularly if analyzed quantitatively.

A practical limitation of FDG-PET is that hypometabolism patterns can be ambiguous and difficult to interpret qualitatively.[7] Our experienced visual raters achieved good agreement on FDG, but near perfect agreement interpreting PiB studies. Similar results have been reported by another group[29] and suggest that, at least in a dementia population, qualitative interpretations of PiB scans are more reproducible than FDG reads. Consistent with previous reports,[6] we found that classifying FDG scans quantitatively in reference to a control population enhanced diagnostic accuracy. Several methods for quantifying FDG data to aid with single subject diagnosis are currently available[30] or under development,[31] and our data suggest that adopting quantification into clinical practice would improve the diagnostic utility of FDG-PET. In our study, agreement between qualitative and quantitative classifications was very high for PiB and more modest for FDG. Amyloid PET may thus be better suited than FDG for the current clinical standard of qualitative assessment, since visual reads are both more accurate and more precise when compared to quantitative methods.

Our study has limitations. The gold standard against which PiB and FDG were judged was clinical diagnosis, and histopathologic confirmation was available only for a subset of patients. However, the clinical assessment was comprehensive and performed by clinicians who are highly experienced in evaluating AD and FTLD, and clinical diagnosis was confirmed in all 12 patients with known histopathology. The rates of PiB-negative AD (11%) and PiB-positive FTLD (16%) in our study are similar to rates of clinically misclassified patients in autopsy series,[9,10,32] suggesting that PiB may have outperformed the clinical diagnostic standard in some cases. Additional causes of false-negative PiB scans are likely to include low Aβ burden,[33] high amyloid load in the cerebellar reference region,[34] and failure of PiB to bind amyloid.[35] False-positive PiB scans are likely to represent comorbid Aβ plaques in patients with FTLD or another primary pathology.[36] Indeed, one patient in our study with primary FTLD-TDP and comorbid diffuse plaques had a borderline positive PiB scan (by quantitative criteria), though 3 other autopsy-confirmed FTLD patients with early Aβ deposition were visually and quantitatively PiB-negative.

Patients in our study were recruited at an academic dementia center, were required to meet clinical criteria for AD or FTLD, and were relatively young. Our findings may thus not be generalizable to the more clinically ambiguous patients seen in general practice, or to an older population in which the baseline prevalence of amyloid is higher. Though clinically mild, patients in our study all met criteria for dementia, and future studies are needed to compare the performance of amyloid and FDG-PET in the predementia state, when disease-modifying therapies may have the greatest impact. A disadvantage of amyloid PET not addressed in our study design is that it cannot distinguish between different amyloid-positive (e.g., AD vs dementia with Lewy bodies) or amyloid-negative diseases (e.g., FTLD subtypes, psychiatric mimics of FTLD), while MRI and FDG-PET may help in differentiating these conditions.

Though widespread use of PiB is not feasible due to the short half-life of the carbon-11 isotope (20 minutes), new amyloid tracers labeled with fluorine-18 ($t_{1/2}$ = 110 minutes) have thus far performed comparably to PiB[37–39] and could be produced and distributed for clinical use. Future studies are needed to compare the diagnostic performance of amyloid imaging to CSF biomarkers, which have also shown promise in differentiating AD and FTLD.[40] While molecular biomarkers will never replace a

thoughtful clinical evaluation, their development heralds a new era in which core pathologic features of neurodegeneration can be directly measured and incorporated into clinical decision-making. This will doubtlessly increase diagnostic accuracy during life, a critical first step toward developing effective disease-specific therapies for these devastating illnesses.

AUTHOR CONTRIBUTIONS

Dr. Rabinovici, Dr. Jagust, Dr. Miller, and Dr. Rosen designed the study. Dr. Rabinovici, Dr. Jagust, Dr. Rosen, Dr. Alkalay, Dr. Kornak, Dr. Furst, Dr. Mormino, Dr. O'Neil, Dr. Janabi, Dr. Huang, Dr. DeArmond, Dr. Trojanowski, Dr. Grinberg, Dr. Gorno-Tempini, Dr. Seeley, Dr. Miller, M.E. Growdon, N. Agarwal, A. Karydas, and J.Y. Jang analyzed and interpreted data. Dr. Kornak and Dr. Rabinovici performed statistical analysis. Dr. Rabinovici drafted the manuscript. Dr. Jagust, Dr. Miller, Dr. Rosen, Dr. Alkalay, Dr. Furst, Dr. Mormino, Dr. Trojanowski, Dr. Grinberg, Dr. Gorno-Tempini, and Dr. Seeley edited the manuscript for intellectual content. The final manuscript was reviewed and approved by all authors.

ACKNOWLEDGMENT

The authors thank the patients and their families for their participation and dedication to research; Suzanne Baker, Victoria Beckman, Jennifer Kluth, Amynta Hayenga, Cindee Madison, and Irene Yen for administrative and technical support; Nick Vandehey for radiochemistry; and Giovanni Coppola and Daniel Geschwind for genetic testing.

DISCLOSURE

Dr. Rabinovici serves on scientific advisory boards for Novartis and GE Healthcare; received a speaker honorarium from Novartis; and receives research support from the NIH/NIA, the Alzheimer's Association, and the John Douglas French Alzheimer's Foundation. Dr. Rosen serves on a scientific advisory board for Avanir Pharmaceuticals; receives publishing royalties for *The Emotional Brain* (Oxford University Press); and receives research support from the NIH (NIA, NINDS, DHS/ADP/ARCC) and the Larry L. Hillblom Foundation. Dr. Alkalay reports no disclosures. Dr. Kornak receives research support from a UCSF Pilot Research Award for Junior Investigators, the NIH (NCRR, NIA, NINDS, NCI), the US Department of Defense, and the National Multiple Sclerosis Society. Dr. Furst, N. Agarwal, and Dr. Mormino report no disclosures. Dr. O'Neill receives research support from Genzyme Corporation, the US Department of Energy, the US Army Medical Research & Materiel Command, and the NIH. Dr. Janabi has received research support from the NIH. A. Karydas, M.E. Growdon, J.Y. Jang, Dr. Huang, and Dr. DeArmond report no disclosures. Dr. Trojanowski has received funding for travel and honoraria from Takeda Pharmaceutical Company Ltd.; has received speaker honoraria from Pfizer Inc.; serves as an Associate Editor of *Alzheimer's & Dementia*; may accrue revenue on patents re: Modified avidin-biotin technique, Method of stabilizing microtubules to treat Alzheimer's disease, Method of detecting abnormally phosphorylated tau, Method of screening for Alzheimer's disease or disease associated with the accumulation of paired helical filaments, Compositions and methods for producing and using homogeneous neuronal cell transplants, Rat comprising straight filaments in its brain, Compositions and methods for producing and using homogeneous neuronal cell transplants to treat neurodegenerative disorders and brain and spinal cord injuries, Diagnostic methods for Alzheimer's disease by detection of multiple MRNAs, Methods and compositions for determining lipid peroxidation levels in oxidant stress syndromes and diseases, Compositions and methods for producing and using homogenous neuronal cell transplants, Method of identifying, diagnosing and treating alpha-synuclein positive neurodegenerative disorders, Mutation-specific functional impairments in distinct tau isoforms of hereditary frontotemporal dementia and parkinsonism linked to chromosome-17: genotype predicts phenotype, Microtubule stabilizing therapies for neurodegenerative disorders, and Treatment of Alzheimer's and related diseases with an antibody; and receives research support from the NIH/NIA and from the Marian S. Ware Alzheimer Program. Dr. Grinberg serves as an Associate Editor for *Frontiers in Dementia* and *Cell and Tissue Banking*; and receives research support from the John Douglas French Alzheimer's Foundation and the Alzheimer's Association. Dr. Gorno-Tempini receives research support from the NIH (NINDS, NIA), the John Douglas French Alzheimer's Foundation, the Alzheimer's Association, the Larry L. Hillblom Foundation, the Koret Family Foundation, and the McBean Family Foundation. Dr. Seeley receives research support from the NIH, the James S. McDonnell Foundation, the Consortium for Frontotemporal Dementia Research, and the John Douglas French Alzheimer's Disease Foundation. Dr. Miller serves on a scientific advisory board for the Alzheimer's Disease Clinical Study; serves as an Editor for *Neurocase* and as an Associate Editor of *ADAD*; receives royalties from the publication of *Behavioral Neurology of Dementia* (Cambridge, 2009), *Handbook of Neurology* (Elsevier, 2009), and *The Human Frontal Lobes* (Guilford, 2008); serves as a consultant for Lundbeck Inc., Elan Corporation, and Allon Therapeutics, Inc.; serves on speakers' bureaus for Novartis and Pfizer Inc.; and receives research support from Novartis and the NIH/NIA and the State of California Alzheimer's Center. Dr. Jagust has served on a scientific advisory board for Genentech, Inc.; serves as Associate Editor for *Frontiers in Human Neuroscience* and on the editorial boards of *Annals of Neurology*, *Brain Imaging and Behavior*, and *Alzheimer's Disease and Associated Disorders*; receives publishing royalties for *Imaging the Aging Brain* (Oxford University Press, 2009); has served as a consultant for Synarc, Elan Corporation/Janssen Alzheimer Immunotherapy, Genentech, Inc., Abbott, GE Healthcare, Ceregene, Bayer Schering Pharma, Schering-Plough Corp., TauRx Pharmaceuticals, Otsuka Pharmaceutical Co., Ltd., and Merck & Co; and receives research support from the NIH and from the Alzheimer's Association.

Received April 21, 2011. Accepted in final form June 14, 2011.

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