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*Neurology* 2007;68;1205-1212

DOI: 10.1212/01.wnl.0000259035.98480.ed

This information is current as of April 15, 2007

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http://www.neurology.org/cgi/content/full/68/15/1205
**11C-PIB PET imaging in Alzheimer disease and frontotemporal lobar degeneration**

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**Abstract—Background:** The PET tracer 11C-labeled Pittsburgh Compound-B (11C-PIB) specifically binds fibrillar amyloid-beta (Aβ) plaques and can be detected in Alzheimer disease (AD). We hypothesized that PET imaging with 11C-PIB would discriminate AD from frontotemporal lobar degeneration (FTLD), a non-Aβ dementia. **Methods:** Patients meeting research criteria for AD (n = 7) or FTLD (n = 12) and cognitively normal controls (n = 8) underwent PET imaging with 11C-PIB (patients and controls) and 18F-fluorodeoxyglucose (18F-FDG) (patients only). 11C-PIB whole brain and region of interest (ROI) distribution volume ratios (DVR) were calculated using Logan graphical analysis with cerebellum as a reference region. DVR images were visually rated by a blinded investigator as positive or negative for cortical 11C-PIB, and summed 18F-FDG images were rated as consistent with AD or FTLD. **Results:** All patients with AD (7/7) had positive 11C-PIB scans by visual inspection, while 8/12 patients with FTLD and 7/8 controls had negative scans. Of the four PIB-positive patients with FTLD, two had 18F-FDG scans that suggested AD, and two had 18F-FDG scans suggestive of FTLD. Mean DVRs were higher in AD than in FTLD in whole brain, lateral frontal, precuneous, and lateral temporal cortex (p < 0.05), while DVRs in FTLD did not significantly differ from controls. **Conclusions:** PET imaging with 11C-labeled Pittsburgh Compound-B (11C-PIB) helps discriminate Alzheimer disease (AD) from frontotemporal lobar degeneration (FTLD). Pathologic correlation is needed to determine whether patients with PIB-positive FTLD represent false positives, comorbid FTLD/AD pathology, or AD pathology mimicking an FTLD clinical syndrome.

NEUROLOGY 2007;68:1205–1212

Accurately differentiating Alzheimer disease (AD) and frontotemporal lobar degeneration (FTLD) has implications for prognosis and heritability.1,4 Furthermore, currently available symptomatic therapies for AD are often ineffective in FTLD,5 and anti-amyloid-beta (Aβ) treatments under development for AD6 are unlikely to be effective in FTLD. Clinically differentiating AD from FTLD can be challenging given overlapping symptoms and neuropsychological profiles.7–10 Many pathologically proven FTLD cases also meet clinical criteria for AD,7,11,12 while AD pathology can be associated with FTLD clinical syndromes. AD was found to be the pathologic cause of dementia in roughly one-third of patients with progressive aphasia,13 11% of patients with semantic dementia (SemD, the temporal variant of FTLD),14 and in 17% of all patients with an FTLD clinical syndrome.15,16 Thus, diagnostic tools that could more accurately predict pathology would be of great clinical value.

The novel PET tracer [N-methyl-11C]-2-(4’-methylaminophenyl)-6-hydroxybenzothiazole (11C-labeled Pittsburgh Compound-B, or 11C-PIB) is a thioflavin-T analog that at radiotracer concentrations has a high affinity for fibrillar Aβ,17 a pathologic hallmark of AD that is not part of the FTLD pathologic spectrum. 11C-PIB binds specifically to fibrillar Aβ in postmortem AD brains,17,18 but shows a low binding affinity to postmortem brains from controls or patients with non-Aβ dementias, including FTLD.17 11C-PIB can be detected by PET in vivo...
in patients with AD, and has also been used to study patients with mild cognitive impairment and normal controls. However, the utility of \(^{11}C\)-PIB in the differential diagnosis of dementia remains unknown. Here we report results of a pilot study investigating the utility of \(^{11}C\)-PIB PET in distinguishing clinically diagnosed AD and FTLD. A priori, we hypothesized that patients with AD would show cortical \(^{11}C\)-PIB retention and patients with FTLD would not.

**Methods.** **Subject selection.** Patients were recruited from AD and FTLD research cohorts followed at the University of California San Francisco Memory and Aging Center (UCSF MAC). All patients had at least one clinical evaluation at the MAC, including a history and physical examination by a neurologist, a structured caregiver interview administered by a nurse, and a comprehensive battery of neuropsychological tests. Patients’ functional status was measured using the Clinical Dementia Rating Scale (CDR). MRI scans acquired clinically or through research were reviewed for all patients at the time of diagnosis. Clinical diagnoses were assigned at a multidisciplinary conference using standard research criteria for AD, the FTLD clinical subtypes frontotemporal dementia (FTD), semantic dementia (SemD), and progressive aphasia (PA), and amyotrophic lateral sclerosis (ALS). Onset of symptoms was determined retrospectively based on the estimated date of the first symptom as identified by patients or caregivers and documented in medical records.

Patients were considered eligible for the study if they met research criteria for AD or FTLD, and did not have significant comorbid medical, neurologic, or psychiatric illness. Control subjects were recruited from the community by advertisement. All were free of significant medical illnesses and were not taking medications deemed to affect cognition. Control subjects were judged to be cognitively normal following an evaluation that included a medical history, functional assessment, neurologic examination, and neuropsychological assessment with a battery of tests similar to those performed by patients. Eligible subjects were recruited between April 2005 and May 2006, and all who consented were enrolled.

The final cohort included 7 patients with AD, 12 patients with FTLD, and 8 normal controls (Table 1). At the time of this report, pathologic confirmation of the diagnosis was available for one patient with FTLD-FTD (autopsy diagnosis of Pick disease\(^{27}\)). In a second patient with familial FTD/ALS, a pathologic diagnosis of FTLD with motor-neuron (ubiquitin-positive, tau-negative) inclusions\(^{28}\) was made in the patient’s deceased brother.

The study was approved by the University of California at Berkeley Campus Committee for the Protection of Human Subjects.

**Radiochemical synthesis.** \(^{11}C\)-PIB was synthesized at the Lawrence Berkeley National Laboratory’s Biomedical Isotope Facility using a previously published protocol. In brief, high specific activity \(^{11}C\)-carbon dioxide produced on an 11 MeV CTI RDS-111 cyclotron was used to synthesize \(^{11}C\)-CH\(_2\). \(^{11}C\)-PIB precursor 2-(4-aminophenyl)-6-methoxymethoxybenzothiazole was prepared using previously described procedures, then methylated with \(^{11}C\)-CH\(_3\)I prior to deprotection to afford the 6-hydroxy compound, \(^{11}C\)-PIB. The final compound was purified by semi-preparative HPLC. Specific activity was determined for every batch, and averaged 4,648 ± 1,214 Ci/mmol. \(^{18}F\)-fluorodeoxyglucose (\(^{18}F\)-FDG) was purchased from a commercial vendor (Eastern Isotopes, Sterling, VA).

**Image acquisition.** PET scans were performed at Lawrence Berkeley National Laboratory using a Siemens ECAT EXACT HR PET scanner in three-dimensional acquisition mode. All 27 subjects (19 patients and 8 controls) underwent PET imaging with \(^{11}C\)-PIB. An average of 16.4 mCi of \(^{11}C\)-PIB (range 9.8 to 19.2 mCi) was injected as a bolus into an antecubital vein. Dynamic acquisition frames were obtained as follows: 4 x 15 seconds, 8 x 30 seconds, 9 x 60 seconds, 2 x 180 seconds, 8 x 300 seconds, and 3 x 600 seconds, for a total of 90 minutes. Most patients (17 of 19) also underwent PET imaging with \(^{18}F\)-FDG. At a minimum of 2

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>AD, n = 7</th>
<th>FTLD, n = 12</th>
<th>Controls, n = 8</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probable AD, n = 6</td>
<td></td>
<td></td>
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<tr>
<td>Possible AD, n = 1</td>
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<td></td>
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</tr>
<tr>
<td>M/F</td>
<td>6.5 (8.2)</td>
<td>6.2 (7.8)</td>
<td>7.1 (7.3)</td>
<td>NS</td>
</tr>
<tr>
<td>Education, y</td>
<td>16.9 (3.4)</td>
<td>13.4 (3.9)</td>
<td>17.0 (2.1)(^*)</td>
<td>NS</td>
</tr>
<tr>
<td>Onset to PET, y</td>
<td>9.1 (2.5)</td>
<td>6.8 (3.4)</td>
<td>N/A</td>
<td>NS</td>
</tr>
<tr>
<td>MMSE</td>
<td>19.3 (7.1)</td>
<td>22.0 (7.9)</td>
<td>29.5 (0.5)(†)</td>
<td>&lt;0.01\‡</td>
</tr>
<tr>
<td>ApoE4 positive</td>
<td>6(\text{a})</td>
<td>2(\text{†})</td>
<td>N/A</td>
<td>&lt;0.01</td>
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<tr>
<td>Mediations</td>
<td></td>
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<tr>
<td>ChEI</td>
<td>7</td>
<td>3</td>
<td>0(\text{a})</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Memantine</td>
<td>7</td>
<td>8</td>
<td>0(\text{a})</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>5</td>
<td>7</td>
<td>3(\text{a})</td>
<td>NS</td>
</tr>
</tbody>
</table>

Continuous variables are presented as means (SD). \(p\) Values correspond to comparisons across all groups.

\(\text{a}\) Data not available for one subject.
\(\text{†}\) Data not available for two subjects.
\(\text{‡}\) \(p < 0.01\) for AD vs controls and FTLD vs controls.

AD = Alzheimer disease; FTLD = frontotemporal lobar degeneration; FTD = frontotemporal dementia; ALS = amyotrophic lateral sclerosis; SemD = semantic dementia; PA = progressive aphasia; MMSE = Mini-Mental State Examination; CDR = Clinical Dementia Rating; ApoE4 = apolipoprotein E4; ChEI = cholinesterase inhibitor; N/A = not available or not applicable; NS = not significant \((p > 0.05)\).
hours following $^{11}$C-PIB injection (six Carbon-11 half-lives), patients were injected with an average of 9.4 mCi of $^{18}$F-FDG (range 8.8 to 10.0 mCi). Six emission frames of 5 minutes each were acquired starting 30 minutes after tracer injection, with the patient resting quietly in a dimly lit room with minimum ambient noise, and eyes and ears unoccluded during tracer uptake. Ten minute transmission scans for attenuation correction were obtained either immediately prior to or following each $^{11}$C-PIB and $^{18}$F-FDG scan. PET data were reconstructed using an ordered subset expectation maximization algorithm with weighted attenuation. Images were smoothed with a 4 mm Gaussian kernel with scatter correction. All images were evaluated prior to analysis for patient motion and adequacy of statistical counts.

Most patients (18 of 19) underwent high resolution MRI scans on a 1.5-T MAGNETOM Vision (Siemens, Iselin, NJ) using a previously published protocol. Patients with multiple MRIs, the MRI closest to the date of the PET scan was used for analysis. Research protocol MRI scans were not available for controls and for one patient.

Image preprocessing and definition of regions of interest. Structural scans (T1-weighted MRIs) were manually reoriented to the anterior–posterior commissure plane and origins were set to the anterior commissure– posterior commissure (ACC) plane. Structural images were coregistered in SPM2 (http://www.fil.ion.ucl.ac.uk/spm) and the resulting gray and white matter images were added to form a brain mask. This mask was then applied to the original MRI to effectively skull-strip the brain. The skull-stripped image was normalized (SPM2 defaults) to the Ch2bet template, a high-resolution skull-stripped single-subject T1-weighted scan in Montreal Neurological Institute (MNI) space. The resulting normalization parameters were then used to perform a reversed (backwards) normalization on a set of MNI space region of interest (ROI) templates that included lateral frontal, lateral temporal, medial temporal, precuneus and posterior cingulate cortices, subcortical white matter, and pons. All templates were a subset of the Automated Anatomic Labeling (AAL) Atlas except the white matter and pons ROIs, which were manually drawn.

The reversed normalization warps MNI space ROIs into native-space. For each patient it involves extraction of a deformation field from the normalization parameters, inversion of the field, and finally application of the obtained inversion to the ROIs. In order to prevent bleeding into CSF areas, the native-space brain mask was applied to all ROIs. The resulting native-space ROIs were then registered and resliced to the mean $^{11}$C-PIB PET image obtained during realignment of the $^{11}$C-PIB frames (see below). Since the segmentation algorithm originally applied to the MRIs occasionally failed to distinguish dura mater or skull from gray matter, we applied an additional brain mask based on the subject’s mean $^{11}$C-PIB image. Finally, all ROIs were overlaid and visually inspected on the subject’s coregistered MNI and $^{11}$C-PIB PET images (see below). Manual editing of ROIs was performed when necessary.

The ROI definition protocol had to be slightly altered for one patient and all eight controls who did not have a structural scan. The Ch2 template (not skull-stripped) and all AAL ROIs were coregistered and resliced to the SPM PET template image. The subject’s native-space mean $^{11}$C-PIB PET image was then normalized to the PET template, and reverse normalization was performed on the ROIs using the procedure described above.

Origins were manually set to AC in all PET frames. $^{11}$C-PIB frames 6 through 34 were coregistered and resliced with SPM2 PET realignment parameters using a mid-scan frame visually judged to best represent the subject’s anatomy (usually number 17) as the reference frame. Frames 1 through 5 were coregistered separately to the mean $^{11}$C-PIB image obtained from realignment, since the frames typically contain a paucity of anatomical information due to low tracer counts. $^{18}$F-FDG scans were realigned with defaults, summed, and subsequently coregistered to the mean $^{11}$C-PIB image.

Image analysis. $^{18}$F-FDG scans were normalized to mean activity in the pons ROI for each subject. For $^{11}$C-PIB, voxel-wise and ROI distribution volume ratios (DVRs) were calculated using Logan graphical analysis package (LIGA) with the pons ROI as reference region. The ROI time–activity curve was used as a reference tissue input function. The cerebellum was chosen as a reference region because it is relatively free of fibrillar plaques in AD, and results obtained with this analysis are similar to those derived from arterial input functions. Kinetic parameters ($T = 35$ to 90 minutes, $k_i = 0.15$ minutes$^{-1}$) were based on previously reported values. In one patient (clinical diagnosis of FTLD-FTD), the cerebellum was missing from many image frames due to patient motion and could not be used as a reference region. A DVR image for this patient was created using the pons ROI as a reference region, since $^{11}$C-PIB binding in the pons does not differ between AD patients and controls, and results obtained with the pons as a reference region are qualitatively very similar to those obtained when cerebellum is used (unpublished observations). The DVR image from this patient was used for visual inspection only, and was excluded from quantitative analyses.

Visual inspection. Voxel-wise $^{11}$C-PIB DVR images from all subjects were qualitatively assessed by an experienced PET investiga-
tor (W.J.J.) blinded to clinical diagnosis. DVRs were visually read as positive or negative for cortical $^{11}$C-PIB. A positive scan was defined as a DVR image in which uptake was significantly greater in cortex than in white matter. Summed $^{18}$F-FDG frames from patients only (not including controls) were visually read by the same investigator in a separate session as consistent with the metabolic pattern of either AD or FTLD. The AD pattern was defined (hypometabolism) by a second blinded investigator could be characterized by hypometabolism in the cerebellum, frontal, parietal, posterior temporal, and posterior cingulate/precuneus cortical regions. Frontal hypometabolism was allowed if it was judged to be less severe than posterior hypometabolism. Conversely, an $^{18}$F-FDG pattern consistent with FTLD was defined as a more severe metabolic lesion in dorsolateral, dorsomedial, and ventromedial frontal or anterior temporal cortex. To assess inter-rater reliability, a second blinded investigator was required. The Kruskal-Wallis equality-of-populations rank sum test was used to compare three groups, and Wilcoxon’s rank sum test was used to compare two groups. Dichotomous variables were analyzed using Fisher exact tests. Inter-rater reliability for visual interpretations was calculated using Cohen’s Kappa. Mean DVR ROI values were compared between and within groups using repeated measures ANOVA (due to the high correlation between ROI DVR values for a given subject), with planned post hoc comparisons between AD and controls, FTLD and controls, and AD and FTLD. Statistical analyses were implemented in SPSS 12.0 for Windows (SPSS Inc., Chicago, IL) and Statistica 6.0 software (StatSoft Inc., Tulsa, OK).

Results. Demographics. Study subjects were well matched for age, gender, and education (table 1). Patients had lower Mini-Mental State Examination (MMSE) scores than controls ($p < 0.01$). AD and FTLD patients were well matched for disease duration and for dementia severity, as measured by the MMSE and CDR. All six patients with AD and AD with apolipoprotein E (ApoE) carriers were carriers of the ApoE4 allele, in comparison to 2 of 10 FTLD patients ($p < 0.01$). Medication use differed significantly between groups, with patients with AD using cholinesterase-inhibitors more frequently than both patients with FTLD and controls, and both AD and FTLD patients using memantine more frequently than controls.

Visual interpretation. Results of PET visual reads by the primary reader are presented in table 2. All seven patients with AD demonstrated cortical $^{11}$C-PIB retention on visual inspection (PIB-positive scan), while 8/12 patients with FTLD and 7/8 controls did not (PIB-negative scan) (figure E-1 on the Neurology Web site at www.neurology.org). The patient with pathologically confirmed Pick disease and the patient with familial FTLD/ALS both had negative $^{11}$C-PIB scans by visual inspection.

Visual reads of $^{18}$F-FDG scans agreed with the clinical diagnosis in 5/6 patients with AD and 8/11 patients with...
FTLD (table 2). $^{11}$C-PIB and $^{18}$F-FDG suggested the same diagnosis (PIB-positive scan and FDG consistent with AD, or PIB-negative scan and FDG consistent with FTLD) in 13/17 patients. In 3/4 cases in which there was a discrepancy, the $^{18}$F-FDG scan suggested FTLD, while the $^{11}$C-PIB scan was positive.

A second blinded reader agreed with the primary visual read on 19/19 patient $^{11}$C-PIB scans (kappa = 1.00) and 15/17 $^{18}$F-FDG scans (kappa = 0.76). Both disparate $^{18}$F-FDG reads occurred in FTLD patients: one who was PIB-positive (read as AD by the primary reader and FTLD by the second reader) and one who was PIB-negative (primary read FTLD, second read AD).

**Qualitative assessment of $^{11}$C-PIB distribution.** Six of seven patients with AD showed a diffuse, symmetric pattern of $^{11}$C-PIB uptake (see figure E-1 for illustration), with tracer retention throughout lateral (dorsolateral and peri-opercular), medial (anterior and mid-cingulate, supplementary motor area [SMA]), and orbital frontal cortex; lateral (anterior and supramarginal gyrus, superior and inferior parietal lobules) and medial (precuneus and posterior cingulate) parietal cortex; lateral temporal cortex (including superior, middle, and inferior temporal gyri); occipital visual association cortex; striatum; and thalamus. Four of seven patients with AD had elevated $^{11}$C-PIB in calcarine cortex. One patient with AD (AD-4) demonstrated an atypical uptake pattern, with $^{11}$C-PIB uptake restricted to dorsal medial (mid-cingulate and SMA) and lateral (superior and middle frontal gyri) frontal cortex, precentral gyrus, and dorsal precuneus (figure E-2). Medial temporal structures were relatively spared in all patients with AD.

The four PIB-positive patients with FTLD all showed a diffuse pattern of tracer uptake (figures E-3 and E-4), with involvement of all of the above-mentioned frontal, parietal, lateral temporal, and occipital regions (including calcarine cortex in three of four patients), striatum, and thalamus. In contrast, the one PIB-positive control had a restricted pattern of uptake, with moderately elevated $^{11}$C-PIB in medial parietal cortex (posterior cingulate and precuneus), and mildly elevated $^{11}$C-PIB in (predominantly medial) frontal cortex.

**PIB-positive patients with FTLD.** Four of 12 clinically diagnosed patients with FTLD had positive $^{11}$C-PIB scans. We retrospectively reviewed these patients’ clinical data in light of the discrepancy between their clinical diagnosis and the $^{11}$C-PIB result.

Two of the PIB-positive patients with FTLD had a clinical diagnosis of FTLD-FTD (figure E-3). At initial presentation, FTLD-4 was a 55-year-old left-handed man with 9 years of profound behavioral changes, including compulsive sorting, disinhibition and socially inappropriate behavior (e.g., stripping naked at a family beach outing, pretending to be blind so that his dog would be allowed on a train). On a neuropsychological battery, he scored 20/30 on the MMSE, and showed deficits in episodic memory (recalled 2/9 words after a 10-minute delay on the California Verbal Learning Test [CVLT]), visual-spatial tasks (could not correctly copy intersecting pentagons, and scored 7/17 on copy of the Modified Rey-Osterrieth design), and executive function (107 seconds to complete modified Trails-B, seven designs/minute on the Delis Kaplan Executive Function Scale [DKEFS] design fluency task). The visual-spatial deficits are unusual for FTD, and are more consistent with AD. However, the degree of behavioral disturbance as measured by the Neuropsychiatric Inventory (NPI) (score of 46) was more typical of FTD. MRI demonstrated predominantly biparietal atrophy, and $^{18}$F-FDG PET (obtained 27 months after initial presentation as part of this study) showed biparietal hypometabolism, and was read by the blinded investigator as consistent with AD (figure E-3).

At presentation, FTLD-1 was a 53-year-old right-handed woman with a 5-year history of short-term memory loss, poor organization and planning skills, and behavioral changes including inappropriate journaling, disinhibition, apathy, and poor insight. On neuropsychological testing, she scored 25/30 on the MMSE, and showed deficits in executive function (two correct lines and three errors in 120 seconds on modified Trails-B, one design in 1 minute on DKEFS design fluency), working memory (digit-span backwards of two), episodic memory (3/9 free recall at 10 minutes on the CVLT), naming (10/15 on the Boston Naming Test [BNT]), and verbal fluency (five animals and eight D words in 1 minute), a pattern consistent with either AD or FTD. However, her total NPI score (7) was low compared to other patients with FTD. MRI showed predominantly frontal atrophy, but $^{18}$F-FDG PET (obtained 1 year after initial presentation) showed prominent biparietal hypometabolism and was read by the blinded investigator as consistent with AD (figure E-3). Of note, on follow-up over 19 months, she demonstrated a significant decline in verbal and visual memory and confrontation naming, changes more consistent with AD than FTD.

The other two PIB-positive patients with FTLD had a clinical diagnosis of FTLD-SemD (figure E-4). At initial evaluation, FTLD-9 was a 58-year-old right-handed woman with a 10-year history of rheumatologic disease (diagnosed as either systemic lupus erythematosus [SLE] or Sjögren syndrome) and 3 years of progressive word-finding difficulties, compulsive video game and solitary playing, and restrictive dieting. Her language was fluent with impoverished content, semantic paraphasic errors, nonspecific noun substitutions, and surface dyslexia and dysgraphia. Neuropsychological testing was notable for an MMSE of 29/30, with profound deficits in naming (3/15 on the BNT), and decreased semantic (five animals) relative

| Table 2 Visual reads (by primary reader) of PET scans |
|-----------------|-----------------|-----------------|
| PET read        | Clinical AD     | Clinical FTLD   | Controls         |
|                 | PIB (+)         | PIB (-)         | PIB (+)          | PIB (-)          |
| FDG–AD          | 5               | 0               | 2               | 1               | 0               | 0               |
| FDG–FTLD        | 1               | 0               | 2               | 6               | 0               | 0               |
| FDG–N/A         | 1               | 0               | 0               | 1               | 1               | 7               |
| Total           | 7               | 0               | 4               | 8               | 1               | 7               |

$^{11}$C-PIB scans were read as positive (+) or negative (−) for cortical PIB, while $^{18}$F-FDG scans were read as consistent with the metabolic pattern of AD or FTLD.

AD = Alzheimer disease; FTLD = frontotemporal lobar degeneration; PIB = $^{11}$C-labeled Pittsburgh Compound B; FDG = $^{18}$F-labeled fluorodeoxyglucose; N/A = not available.
to lexical (eight D words) fluency. Overall, her clinical and neuropsychological presentation was classic for SemD.

FTLD-10 was a 63-year-old right-handed woman with 4.5 years of progressive word-finding difficulties, short-term memory loss, impaired judgment, loss of empathy, and disinhibited behavior. Her language was fluent with impoverished content, occasional semantic paraphasic errors, poor confrontation naming, and surface dysgraphia. Neuropsychological testing revealed an MMSE of 26/30, with deficits in episodic memory (0/9 10 minute free recall on the CVLT), verbal fluency (five animals and five D words per minute), and naming (10/15 on the BNT). This profile could be consistent with either SemD or AD, though naming performance was high for SemD. Both PIB-positive SemD patients showed left greater than right anterior temporal atrophy on MRI, and 18F-FDG PET (obtained 3.5 years [FTLD-9] and 3 months [FTLD-10] after presentation) demonstrated left greater than right anterior temporal hypometabolism (figure E-4). Both 18F-FDG scans were read by the blinded investigator as consistent with FTLD.

In summary, out of four patients clinically diagnosed with FTLD with positive 11C-PIB scans, one patient had a neuropsychological profile more consistent with AD (albeit with profound behavioral disturbances), one had a classic profile for SemD, and two patients had cognitive profiles that could be consistent with either AD or FTLD. In both PIB-positive patients with FTLD, 11C-PIB and 18F-FDG agreed with each other in suggesting a diagnosis of AD, and disagreed with the clinical diagnosis of FTD. In contrast, both PIB-positive SemD patients had 18F-FDG scans consistent with FTLD.

Quantitative analysis of 11C-PIB and 18F-FDG. Scatterplots of 11C-PIB whole brain and ROI DVR values are presented in figure 1. Differentiation of scans visually read as PIB-positive and PIB-negative provides a more informative representation of the data than simple clinical diagnosis. Patients with AD generally had higher DVR values than controls in the whole brain and in cortical ROIs. Patient AD-4, who qualitatively demonstrated restricted dorsal 11C-PIB uptake (figure E-2), had an elevated DVR in lateral frontal cortex, whereas DVR values in other ROIs were similar to controls. There was greater overlap between groups in medial temporal cortex, where there is a relatively low burden of Aβ plaques in AD. Patients with FTLD showed a bimodal distribution of DVRs in the whole brain and in cortical ROIs: patients with negative 11C-PIB scans had DVRs that were comparable to controls, while patients with positive 11C-PIB scans had DVRs that were similar to AD. As has been reported previously, we found intermediate levels of 11C-PIB binding in both patients and controls in subcortical white matter and pons (latter not shown). This is thought to be due to nonspecific binding of 11C-PIB to white matter, though the precise nature of this binding has not yet been determined.

Comparison of mean DVR values using repeated measures ANOVA revealed main effects for both diagnosis [F(2,23) = 4.85, p < 0.05] and ROI [F(7,161) = 20.57, p < 0.001] with an interaction [F(14,161) = 3.88, p < 0.001]. Planned comparisons demonstrated elevated DVRs in AD vs FTLD in whole brain (p < 0.05), lateral frontal (p < 0.05), precuneus (p < 0.05), and lateral temporal (p < 0.05) ROIs. Similarly, DVRs in AD were higher than controls in whole brain (p < 0.01), lateral frontal (p < 0.01), precuneus (p < 0.01), and lateral temporal (p < 0.01) ROIs, with a non-significant trend in posterior cingulate (p = 0.08). Contrary to previous reports, we found higher DVRs in subcortical white matter in AD compared to controls (p < 0.05) and FTLD (p < 0.05), possibly due to cortical contamination of the white matter ROI as a result of the normalization procedure. DVRs in medial temporal cortex and pons were not significantly different between groups. FTLD DVR values did not significantly differ from controls in any of the ROIs.

Scatterplots of 18F-FDG normalized activity are presented in figure 2. Patients with FTLD are split by clinical subtype given the distinct patterns of 18F-FDG uptake typical of each FTLD variant. As expected, patients with AD tended to have lower 18F-FDG uptake than patients with FTLD in the posterior cingulate and precuneus, and patients with SemD were most severely affected in the temporal lobes. There was considerable overlap between AD and FTLD in lateral frontal and medial temporal ROIs.
Consistent with the visual interpretations, the two PIB-positive patients with FTD had low 18F-FDG uptake in posterior cingulate and precuneus. Interestingly, PIB-negative patients with SemD had lower 18F-FDG uptake in these AD-specific regions than PIB-positive SemD patients. Statistics were not performed on 18F-FDG normalized values given the small number of patients in each group once patients with FTLD were separated by clinical subtype.

**Discussion.** In this study we report preliminary results of PET imaging with the Aβ ligand 11C-PIB in patients with AD and FTLD. In vitro studies suggest that 11C-PIB is highly specific for Aβ fibrils, but the specificity of 11C-PIB in distinguishing AD from non-Aβ dementias such as FTLD has not been demonstrated in vivo. We found that 11C-PIB was sensitive for the diagnosis of AD, with all seven patients with AD having positive 11C-PIB scans. Unexpectedly, a subset of patients with FTLD (4 of 12) also had positive 11C-PIB scans, even though Aβ deposition is not part of the FTLD pathologic spectrum.

There are several potential explanations for cortical 11C-PIB uptake in these patients. First, 11C-PIB may be binding to something other than Aβ in these patients. However, current evidence suggests that at PET tracer concentrations, 11C-PIB is highly specific for Aβ amyloid fibrils. In the one study that tested in vitro 11C-PIB binding to postmortem samples from patients with non-Aβ dementias (including three patients with FTLD), 11C-PIB showed a very low binding affinity to frontal cortex homogenates, with tenfold lower binding than was seen in AD homogenates.67 Significantly, both patients in our study with pathologically confirmed FTLD (Pick disease, a tauopathy, in one subject, and FTLD with motor-neuron [tau-negative ubiquitin-positive] inclusions in another subject’s affected sibling) had negative 11C-PIB scans.

A second explanation is that PIB-positive patients with FTLD have comorbid AD and FTLD pathology, with FTLD pathology driving the clinical syndrome. Aβ plaques can be found on autopsy or detected by 11C-PIB in nondemented elderly, and comorbid AD and FTLD pathology, while relatively uncommon, can be seen on autopsy. The possibility of comorbid amyloid (Aβ or other) is particularly intriguing in patient FTLD-9, since both SLE and Sjögren syndrome are associated with secondary amyloidosis and decreases in CSF Aβ42 levels have been reported in patients with SLE. The relatively young ages of the other PIB-positive patients with FTLD in this study (54 to 63) makes incidental or age-related Aβ less likely, but does not exclude this possibility.

A third consideration is that PIB-positive patients with FTLD truly have underlying AD pathology mimicking an FTLD clinical phenotype. Supporting this possibility, three of four PIB-positive patients with FTLD had cognitive profiles that were more or equally suggestive of AD, and two of four had 18F-FDG scans that were classic for AD. The proportion of PIB-positive patients with FTLD in this study is similar to the proportion of patients with a clinical diagnosis of FTLD who are found to have AD pathology postmortem. Clinical criteria, neuropsychological profiles, and structural and functional imaging may all fail to correctly predict underlying pathology when neurodegeneration does not adhere
to common anatomic patterns. It is precisely in these cases that molecular imaging with 11C-PIB may prove to be most useful.

While the major objective of this study was to compare 11C-PIB binding in AD and FTLD, we also included a number of cognitively normal controls for comparison. Though there was a nonsignificant trend for higher cortical DVRs in FTLD vs controls, this trend was driven by the four PIB-positive patients with FTLD whose cortical DVRs were similar to those of AD (figure 1). The remaining PIB-negative patients with FTLD (including the two pathologically confirmed cases) had 11C-PIB scans that were both qualitatively and quantitatively indistinguishable from those of PIB-negative controls. Consistent with other series,16,32 one of our eight controls had a qualitatively positive 11C-PIB scan. This 74-year-old community-dwelling volunteer had no cognitive complaints, and an MMSE of 30. Compared to other controls, 11C-PIB uptake was moderately elevated in posterior cingulate and precuneus, and mildly elevated in frontal cortex (figure 1). A similar, intermediate pattern of 11C-PIB uptake has been previously reported in nondemented older controls.22

We also sought to compare the results and reliability of 11C-PIB to 18F-FDG PET, which has an established role in the evaluation of dementia and specifically in the differentiation of FTLD and AD.37-40 We found that 11C-PIB and 18F-FDG agreed on the diagnosis in most, but not all (13/17) patients. This result was not unexpected, since 18F-FDG reflects topographic patterns of changes in metabolism, rather than the pathology that underlies these changes. Furthermore, we found that inter-rater reliability was higher for visual interpretations of 11C-PIB (kappa = 1.00) than for 18F-FDG (kappa = 0.76). These findings suggest that in a dementia population, 11C-PIB visual interpretations (which depend on determining the presence or absence of tracer activity in cortex) are highly reproducible, more so than visual reads of 18F-FDG scans, which rely on the interpretation of occasionally ambiguous patterns. For the purpose of diagnosis, PIB may be useful as a qualitative technique (in addition to its quantitative applications in research), which would greatly increase its applicability to the community setting. Further studies are needed to assess whether this degree of reproducibility is maintained across patient populations and clinical settings.

The regional distribution of 11C-PIB uptake in our AD and PIB-positive FTLD patients was similar to the distribution described in previous studies of 11C-PIB in AD.18,53,54 However, one patient with AD (AD-4) showed an atypical pattern of tracer uptake restricted to dorsomedial and dorsolateral prefrontal cortex and dorsal precuneus (figure E-2). To our knowledge, this pattern has not been previously reported. Clinically, this 58-year-old left-handed man presented 7 years earlier with visual-spatial dysfunction, followed 1 year later by short-term memory loss. He was ApoE4 homozygous. Neurologic examination demonstrated stimulus-bound behavior, partial Balint and Gerstmann syndromes, and ideomotor apraxia. Neuropsychological testing showed a typical AD amnestic pattern; however, there were greater than expected deficits in working memory, set-shifting, response inhibition, constructional praxis, and spatial localization. 18F-FDG PET demonstrated bilateral parietal and temporal and right frontal hypometabolism (figure E-2). Thus, in this case of early-onset AD, prominent executive dysfunction was seen in association with disproportionately frontal 11C-PIB uptake, while severe biparietal dysfunction better agreed with the pattern of 18F-FDG hypometabolism. Notably, three younger PIB-positive patients in this study (including another ApoE4 homozygote) showed the more typical, diffuse pattern of 11C-PIB uptake. Further studies are required to define the relationships between age at disease onset, genetic factors, cognitive dysfunction, and amyloid deposition patterns in AD.

The main limitations of this study are the relatively small number of subjects, and the assignment of diagnosis based on the imperfect gold standard of clinical criteria. Thus, limited conclusions can be drawn about the sensitivity and specificity of 11C-PIB in distinguishing between AD and FTLD. Nevertheless, our pilot study suggests that 11C-PIB may be useful for differentiating between these two disorders, and for identifying patients with atypical clinical presentations of AD pathology. Therefore, a definitive study of 11C-PIB in AD and FTLD, with larger patient cohorts, is worth pursuing. Given the potential pitfalls of diagnostic misclassification and mixed pathology, our findings underscore the importance of autopsy confirmation in future studies of 11C-PIB in the differential diagnosis of dementia.

Acknowledgment
The authors thank Dr. William W. Seeley for critical review of this article and Victoria Beckman and Daniela Pavlic for administrative support.

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11C-PIB PET imaging in Alzheimer disease and frontotemporal lobar degeneration


Neurology 2007;68;1205-1212
DOI: 10.1212/01.wnl.0000259035.98480.ed

This information is current as of April 15, 2007

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