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[11C]PIB in a nondemented population
Potential antecedent marker of Alzheimer disease

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Abstract—Background: Beta-amyloid (Aβ) plaques are the hallmark of Alzheimer disease (AD). A PET imaging tracer that binds to Aβ plaques in vivo, N-methyl-[11C]2-(4'-methylaminophenyl)-6-hydroxybenzothiazole (or [11C]PIB for “Pittsburgh Compound-B”), has significantly higher binding in subjects diagnosed with dementia of the Alzheimer type (DAT) compared to nondemented controls. The authors used this imaging technique to investigate whether abnormal binding occurs in clinically normal individuals, prior to the development of cognitive changes. Methods: Forty-one nondemented subjects (age range 20 to 86 years) and 10 patients with DAT (age range 66 to 86 years) underwent [11C]PIB PET scanning. Results: Patients with DAT had elevated BP values vs nondemented subjects (age range 20 to 86 years) and 10 patients with DAT (age range 66 to 86 years) underwent [11C]PIB PET scanning. Regions of interest were drawn on the MRI over the cerebellar, prefrontal, lateral temporal, occipital, gyrus rectus, precuneus, and striatal cortex. Binding potential values (BPs), proportional to the density of [11C]PIB-Aβ binding sites, were calculated using the Logan graphical analysis and the cerebellar cortex for a reference tissue. Conclusions: Elevated [11C]PIB binding in nondemented subjects suggests that [11C]PIB amyloid imaging may be sensitive for detection of a preclinical Alzheimer disease state. Longitudinal studies will be required to determine the association of elevated [11C]PIB binding and risk of developing dementia of the Alzheimer type.

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Several radiotracers with high affinity to beta-amyloid (Aβ) plaques have been developed for the purposes of in vivo human imaging.1-9 One of these tracers, N-methyl-[11C]2-(4'-methylaminophenyl)-6-hydroxybenzothiazole (or [11C]PIB for “Pittsburgh Compound-B”), in preclinical evaluation demonstrated rapid diffusion across the blood–brain barrier, very high affinity to a single binding site on synthetic Aβ (KD = 4.7 nM), and very high affinity to a single binding site to homogenates of frontal cortex from brains with Alzheimer disease (AD) (KD = 1.4 nM).8 The first human studies of [11C]PIB reported significantly increased uptake in individuals with dementia of the Alzheimer type (DAT) compared to healthy controls4,11 although the sample sizes were relatively modest (16 DAT subjects, 6 old controls, and 3 young controls). PET images of [11C]PIB in DAT subjects indicated widespread increased tracer uptake in neocortical regions with relative sparing of the occipital and sensory/motor cortices and with little uptake in the cerebellar cortex.

The capability to image Aβ plaque burden in vivo has potential implications for the diagnosis and management of AD. One application may be in the identification of the neuropathologic changes of AD in clinically normal individuals, prior to the development of cognitive changes.12-16 We evaluated the potential for PET [11C]PIB imaging to detect this putative preclinical AD state of [11C]PIB in vivo in nondemented older subjects. For comparison purposes, and to extend the original findings,11 we also performed PET [11C]PIB imaging in a group of DAT subjects.

Methods. Human subjects. Ten subjects with DAT and 41 subjects with no evidence for cognitive impairment gave written informed consent and underwent PET imaging. All assessment and imaging procedures were approved by Washington University’s Human Studies Committee. Both the DAT and the nondemented individuals (except for three subjects who were <30 years old) were community dwelling volunteers enrolled in the Washington University AD Research Center (ADRC). The assessment protocol has been described.17,18 In brief, an experienced clinician conducts semi-structured interviews with both the subject and an informant to assess potential impairment in the subject’s cognitive and functional performance. A neurologic examination of the subject

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also is obtained. The clinician determines the presence or absence of dementia and rates the severity in accordance with the Clinical Dementia Rating (CDR) where CDR 0 indicates no dementia and CDR 0.5, 1, 2, and 3 indicate very mild, mild, moderate, and severe dementia. The clinical diagnosis of DAT is in accordance with standard criteria and is verified by the neuropathologic diagnosis of AD in 93% of cases. Although elsewhere the CDR 0.5 individuals in our ADRC may be considered to have mild cognitive impairment, they fulfill our diagnostic criteria for very mild DAT and at autopsy overwhelmingly have neuropathologic AD. An independent psychometric battery is administered after the clinical evaluation and CDR assignment. The three young subjects (<30 years) for the PIB study were recruited from the community and were screened to have no neurologic or psychiatric disorders. Demographic data for each subject with CDR and other cognitive scores are itemized in table E-1 on the Neurorology Web site at www.neurology.org.

Imaging. Human brain PET imaging was accomplished using the radiotracer N-methyl-[11C]2-(4'-methylaminophenyl)-6-hydroxybenzothiazole (chemically abbreviated as [11C]6-OH-BTA-1 and referred to as simply [11C]PIB). The preparation of [11C]PIB and the precursor for the radiolabeling studies was carried out according to published literature. The radiochemical synthesis consisted of 1) production of [11C]CH3I (GE PETrace MEI MicroLab) and a custom-built gantry system. Specific activity of [11C]CH3I averaged 4,304 Ci/mmol ± 2,920 Ci/mmol. After obtaining written informed consent from the volunteer (and in the case of DAT subjects, a spouse or other family member also signed informed consent) the subject was positioned either in a Siemens 961 HR ECAT PET scanner (CTI, Knoxville, KY) or in a Siemens ECAT 953 HR ECAT PET scanner (CTI) placed in an antecubital vein. The subject was positioned in the PET scanner such that the cantho-meatal line was approximately 1.0 cm below, and parallel to, the lowest imaging plane. After positioning, a softened thermoplastic mask with enlarged eye holes was placed over the head and secured. After hardening, the mask helps minimize head motion. A transmission scan was obtained to correct attenuation. The room was darkened and noise minimized and the subject had the eyes closed during the scan. Simultaneous with IV injection of 4 to 10 mCi (mean = 10.8 mCi) of [11C]PIB, a 60-minute dynamic PET scan in three-dimensional mode (septa retracted) was initiated (24 × 5 seconds frames; 9 × 20 seconds frames; 10 × 1 minute frames; 9 × 5 minutes frames). Anatomic MRI was obtained on each subject and included MPRAge images of the entire brain. The images were then processed to create a high-resolution, low-noise anatomic image data set. Dynamic PET images were reconstructed with the measured attenuation factors and a ramp filter (final image resolution approximately 5 mm full-width half-maximum, or FWHM). Scatter correction using a fully three-dimensional single scatter simulation algorithm was performed. PET-MR within-participant alignment was performed using an in-house cross-modal registration algorithm that minimizes the error function calculated from voxel-by-voxel activity levels, similar to maximizing the correlation matrices. This algorithm emphasizes image gradient and is thus robust for cross-modal data alignment. Within the dynamic PET data, head motion was corrected using the cross-modal alignment, rather than the intramodal alignment, due to the dramatic changes in tissue activity distribution during the scanning time. Alignment to an atlas target was accomplished by registering a single individualized template for each region of interest (ROIs) were created for each subject based on their individual MR using ANALYZE (Mayo Clinic, Rochester MN) and then applied to the unblurred PET dynamic data to generate time-activity curves. Brain regions were selected to demonstrate the PET imaging levels of gray matter, thalamic gray matter, putamen, nucleus accumbens, and brainstem. Both cerebellum and brainstem were chosen as regions with very low specific binding of PIB for use as reference regions. The white matter region was included as it has been previously shown that white matter has different levels of nonspecific binding than cerebellum. Specific regions were as follows. Prefrontal cortex: the cortical gray matter of the superior and middle frontal gyri (Brodmann area [BA] 9, 10, 11, 46) was manually traced in transverse sections, starting at the beginning of the genu of the corpus callosum and continuing rostrally for 2 cm. The anterior cingulate gyrus was excluded. Lateral temporal cortex: the cortical gray matter of the superior and middle temporal gyri (BA 22 and 21) was manually traced in coronal sections, starting at 24 mm and ending at 46 mm (y axis) in Talairach atlas coordinates. Precuneus: in sagittal sections, the posterior cingulate gyrus was traced beginning in each hemisphere as close as the midline as the region was visible and continuing 1 cm laterally. The posterior boundary of the region was the parieto-occipital sulcus, and the region included the posterior portion of BA 7 and 31. The posterior cingulate gyrus was excluded. Brainstem: the brainstem was traced precisely in transverse sections using visually chosen thresholds to outline the white matter. The clinician determines the presence or absence of DAT to the input function. While the input function is often a plasma time-activity curves from this “reference” region as the input function for processing the other cortical regions of the brain. As previously shown that white matter has different levels of nonspecific binding than cerebellum, as regions with very low specific binding of PIB for use as reference regions. DAT was defined as a significant difference between the groups, our intention was to optimize the ability to detect elevated PIB uptake in a subset of nonnodemented subjects. Eight ROIs were created in each subject. These were prefrontal cortex, lateral temporal cortex, pre-
was selected as a reference region. It has been reported that with PIB this reference tissue approach using the cerebellar cortex as the input function yields highly similar rank order results when compared to using the metabolite-corrected blood activity.\textsuperscript{22,23} In this comparison the approach using Logan graphical analysis with cerebellar input yielded in DV values slightly less than those with metabolite-corrected blood activity, but had superior test-retest reproducibility and larger effect sizes when contrasting a nondemented group with a DAT group.\textsuperscript{21} To express the regional binding values in a manner proportional to the number of binding sites, the binding potential, or BP, was calculated\textsuperscript{34} by the equation \( BP = DV - 1 \).

An additional aspect of the Logan graphical analysis using a reference tissue is that a \( k_2 \) value, which is an estimate of the rate of washout of the tracer from the reference tissue, must be assumed.\textsuperscript{30} We set a value of 0.2/minute in all analyses, but tested a wide range of values of \( k_2 \) using the data from several subjects. In datasets from both nondemented subjects and those with DAT, we found that varying \( k_2 \) over a 10-fold range (0.05 to 0.50/minute) had minimal impact on the resulting DV calculation (less than a 5% total variation in all regions examined).

### Results. Subjects.

The 10 DAT subjects had a mean age of 77.8 (SD \( \pm \) 6.57 years, range 66 to 86 years). Five DAT subjects were CDR 0.5 and five were CDR 1. The 41 nondemented subjects had a mean age of 65.3 (\( \pm \) 16.13, range 20 to 86 years). Twenty nondemented subjects were similarly aged with the DAT subjects; these 20 had a mean range 20 to 86 years). Twenty nondemented subjects were not intended to be an average of the entire brain cortex, but only to sample a priori from areas that have high PIB uptake in the DAT subjects (based on visual inspection of figure 1). The MCBP values for the DAT subjects and the values for the nondemented subjects are shown in figure 2. The mean MCBP value for the DAT group was 0.633 \( \pm \) 0.351 and for the nondemented group was 0.052 \( \pm \) 0.169; a difference that was significant (\( p < 0.0001 \)). The MCBP of those older nondemented subjects in the same age range as the DAT group (66 to 86 years; \( n = 20 \)) also had a lower mean value (0.098 \( \pm \) 0.241) which was different from the DAT group (\( p < 0.0001 \)).

Inspection of the individual PIB uptake data in figure 2 shows that 9 of 10 subjects judged to have DAT by clinical criteria had clearly elevated MCBP value. One of the 10 DAT subjects had negligible MCBP. Upon review of the PET images of this subject, there was no evidence of increased PIB uptake in any region of the brain (not shown), confirming that the low MCBP was not the result of a sampling error. The nondemented subjects generally had values close to zero for PIB specific binding, as measured by BP values (figure 2 and table E-1). However, there were exceptions. Two nondemented subjects (72 years and 74 years) had elevated MCBP values for PIB uptake that were within the same range as seen in the 9 DAT subjects with elevated PIB binding (designated “Hi-PIB”). Visual examination of their PET PIB images shows the same distribution of PIB as in the DAT subjects (figure 3). Two additional nondemented subjects (61 years and 77 years) had moderately elevated MCBP values of 0.299 and 0.227 (designated “Mod-PIB”). (A third nondemented subject had a borderline MCBP value of 0.183.) However, upon review of the specific BP values in these subject groups, there is a suggestion that the precuneus is elevated to a greater percentage in the two nondemented Mod-PIB subjects (figure 4). For example, the precuneus BP values of the DAT patients and the nondemented Hi-PIB subjects average \(<40\%\) higher than the average BP values for prefrontal and temporal regions of these subjects. In contrast, the precuneus BP values of the two nondemented Mod-PIB subjects are \(>125\%\) higher than their prefrontal and temporal BP values.

The psychometric performances of the two “Hi-PIB” and two “Mod-PIB” nondemented individuals as a group did not differ from those of the PIB-negative nondemented individuals age 60 years or older (cognitive assessments obtained within 12 months of PET PIB imaging) (table E-2).

### Discussion.

This study replicates and extends the original findings in human subjects\textsuperscript{11}: with few exceptions, \([^{11}\text{C}]\)PIB retention corresponds to the clinical diagnosis of DAT, and the absence of \([^{11}\text{C}]\)PIB retention corresponds to nondemented status. Second, quantitation of \([^{11}\text{C}]\)PIB binding using only the noninvasive reference tissue model of the Logan graphical analysis\textsuperscript{30} clearly distinguishes between DAT and nondemented subjects, expanding on recently published work.\textsuperscript{33}

Third, we found that the precuneus region of DAT subjects has the highest average BP of all gray matter regions examined. In addition, we found that the precuneus also had the highest regional BP values in
the nondemented subjects who had elevated MCBP. Furthermore, the subjects with most mildly elevated MCBP values had the highest uptake in the precuneus relative to other brain regions. While these data are preliminary, we suggest that the precuneus may be a critical early area of involvement in AD.

Fourth, while longitudinal studies are needed for confirmation, these data support the hypothesis that...
[11C]PIB Aβ plaque imaging can detect the pathologic changes of AD prior to clinical evidence of dementia. The four nondemented subjects with visual and quantitative evidence of increased [11C]PIB specific binding suggest the presence of Aβ plaques similar to the nondemented subjects found in postmortem studies.

The current data replicate and extend the findings of others that DAT is associated with higher cortical binding of [11C]PIB on PET scanning. Nine of 10 subjects with DAT in our study had clearly elevated PIB binding as measured by BP in multiple regions calculated by the Logan graphical analysis technique and reference tissue model. The data presented here suggest this is a sensitive method for detecting the increased [11C]PIB binding in DAT subjects and yet does not require arterial blood sampling. The consistently high correlation coefficients (>0.99) for all regions is one indication that the model is well-suited to this dataset, but recent refinements in this type of graphical approach should be investigated as these methods may offer some advantages in high noise situations or in subjects with slower than expected tracer transport.

The one DAT subject without elevated PIB uptake by BP (or by visual inspection) had a CDR of 0.5 and a Mini-Mental State Examination (MMSE) score of 26, but did not appear to differ from the other DAT subjects on clinical grounds. A lack of increased PIB uptake in some DAT subjects has been previously described. Possible explanations for a “negative” PIB scan include a misdiagnosis in which the clinical dementia is not due to AD and the pathologic findings of AD with Aβ plaques would not be found on a postmortem examination. The clinical diagnosis of DAT, although confirmed at autopsy in 93% of cases in our ADRC, is not perfect. Other possible, more speculative, explanations include a lack of sufficient Aβ plaques and reduced uptake of [11C]PIB, a reduced affinity of the [11C]PIB for the Aβ plaques in a
particular subject, or a substance interfering with \(^{11}C\)PIB binding, such as a medication. At this time there is no basis for favoring any one of these explanations over the misdiagnosis explanation. Longitudinal clinical (and perhaps postmortem) data will be needed to fully understand the predictive potential for \(^{11}C\)PIB imaging for the presence or absence of AD.

The average \(^{11}C\)PIB activity in all DAT subjects after transformation to stereotactic atlas space (figure 1) suggests a specific pattern of Aβ plaque deposition. For example, in these subjects the entire frontal lobe was not uniformly involved. The prefrontal cortex had visually higher \(^{11}C\)PIB uptake than insular cortex, which was higher than motor cortex. Within the basal ganglia, the striatum appeared to have higher average PIB uptake than the thalamus. Within midline structures, the precuneus had higher average PIB uptake than the posterior and anterior cingulate cortices (although the precuneus is similar to the medial prefrontal cortex). Future work should more systematically explore the neuroanatomic distribution of \(^{11}C\)PIB deposition in DAT. In that regard, it has been noted\(^{26}\) that \(^{11}C\)PIB uptake has distinct overlap with the distribution of the hypometabolism and atrophy in patients with early AD as well as the default\(^{28}\) and memory retrieval systems\(^{29}\) in young adults. The implications of this convergence of \(^{11}C\)PIB binding with functional and structural changes has been discussed.\(^{28}\)

Most nondemented subjects in this study had negligible \(^{11}C\)PIB specific binding and thus no evidence for Aβ plaques. However, four nondemented subjects showed definite evidence of elevated PIB retention. In the subset of 20 nondemented subjects matched for age to our DAT subjects (range 66 to 86 years), two had clearly elevated PIB uptake (similar to that seen in the DAT subjects) and one had moderately elevated PIB uptake. These three subjects had CDR scores of 0 and MMSE scores of 30, 25, and 30. In addition, another CDR 0 subject (age 61 years) with a MMSE score of 28 had moderately elevated MCBP values. We suggest that the presence of increased \(^{11}C\)PIB uptake correlates with the presence of Aβ plaques in all four of these nondemented subjects. Other possible explanations, such as \(^{11}C\)PIB binding to other (not Aβ) binding sites, are unlikely given the similarity of the binding distribution to the DAT subjects and the known selectivity of \(^{11}C\)PIB.\(^{4,40}\)

It is also possible that the four subjects with increased \(^{11}C\)PIB uptake may have unrecognized DAT. The cognitive performances of these subjects, however, do not support this explanation. For example, when compared to similarly aged nondemented subjects without increased \(^{11}C\)PIB uptake, the performances of the four subjects did not differ for MMSE\(^{41}\) \((p = 0.482)\), Selective Reminding Test\(^{42}\) \((p = 0.837)\), Word Fluency\(^{43}\) \((p = 0.405)\), Trailmaking B\(^{44}\) \((p = 0.838)\), or Digit Symbol from the Wechsler Adult Intelligence Scale\(^{45}\) \((p = 0.985)\) (table E-2).

That some nondemented subjects have increased \(^{11}C\)PIB binding is not surprising. Several reports describe substantial numbers of Aβ plaques at autopsy in individuals without evidence for cognitive impairment or dementia.\(^{14,46-48}\) We found substantial densities of Aβ plaques and other lesions sufficient to meet neuropathologic criteria for AD in 7 of 26 carefully studied nondemented subjects older than 75 years at death, suggesting a preclinical AD pathologic state.\(^{14}\) The detection of Aβ plaques by in vivo \(^{11}C\)PIB imaging in four nondemented subjects in this study is consistent with a preclinical stage of AD and supports the ability of PET to detect the condition with \(^{11}C\)PIB. However, the likelihood of clinically normal subjects with increased \(^{11}C\)PIB binding to eventually develop DAT can only be answered by longitudinal clinical studies.

A visual inspection of the nondemented subjects with mildly elevated \(^{11}C\)PIB uptake by MCBP values demonstrates subtle increases in precuneus PIB uptake without obvious uptake in the prefrontal regions and the gyrus rectus. Review of the mean BP values on a region-by-region basis (figure 4) suggests that the precuneus is involved early when there is PIB uptake. Further studies are needed to confirm this preliminary finding and its relationship to later development of widespread PIB uptake similar to figure 1. For the detection of preclinical AD, involvement of certain brain regions (e.g., precuneus) may be more predictive than other regions (e.g., striatum) that may be involved later in the disease. The regional pattern of early involvement of PIB uptake also may further our understanding of the development of Aβ plaques.

We used the noninvasive Logan graphical analysis with reference tissue input function to demonstrate significantly increased \(^{11}C\)PIB binding in DAT subjects compared with nondemented individuals. The data indicate involvement of the precuneus region in early stages of the AD process as demonstrated by increased PIB binding compared with binding in other regions, suggesting a potentially critical role of the precuneus in the pathophysiology of AD. We also found that some nondemented controls have elevated PIB uptake similar to, or approaching that of, PIB uptake in DAT subjects, supporting the hypothesis that PIB could be used to detect the preclinical stage of AD.

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