Protein Binding in Patients With Late-Life Depression

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Context: Depression has been identified as a risk factor and a prodrome of dementia. Common neurobiological mechanisms may underlie this clinical and phenomenologic overlap.

Objective: To examine and compare protein (amyloid and tau) binding in critical brain regions in patients diagnosed as having late-life major depressive disorder (MDD) and healthy control individuals using 2-(1-{6-[{(2-[18F]fluoroethyl)}(methyl)-amino]-2-naphthyl}ethylidene) malononitrile ([18F]FDDNP) positron emission tomography.

Design: A cross-section neuroimaging study using positron emission tomography.

Setting: University of California, Los Angeles.

Patients: Our samples comprised 20 patients diagnosed as having MDD and 19 healthy control individuals of comparable age, sex, and educational level.

Main Outcome Measure: Relative distribution volume in regions of interest was used as the measure of [18F]FDDNP binding in all study participants.

Results: When compared with controls, [18F]FDDNP binding was significantly higher overall and in the posterior cingulate and lateral temporal regions in the MDD group.

Conclusions: These findings suggest that neuronal injury associated with higher protein load in critical brain regions might provide a mechanism in the pathophysiologic manifestation of MDD in late life and have implications for the therapeutics of depression in elderly individuals.

Arch Gen Psychiatry. 2011;68(11):1143-1150
logic study\textsuperscript{12} identified prior depression, including clinically significant nonmajor forms of the disorder, as a risk factor for AD. The study, based on a population-based sample, reported that prior depression increased the risk of developing AD after controlling for age, sex, educational level, and premorbid cognition. The Religious Orders Study\textsuperscript{10} identified baseline depression as predictive of the subsequent development of AD in a sample of more than 600 elderly individuals. In this study, depressive symptoms were associated with a decline in episodic memory and spatial ability but not in semantic or working memory. The Multi-Institutional Research in Alzheimer's Genetic Epidemiology study\textsuperscript{17} analyzed data from a sample of 4046 individuals and concluded that although depressive symptoms were associated with the development of AD, the risk was greater when depression occurred in the year immediately before the onset of cognitive impairment. This raises the possibility that depressive symptoms may be a prodrome of AD in specific clinical samples.

Earlier reports from Alexopoulos and coworkers\textsuperscript{18} identified patients with MDD and executive function impairment as more likely to develop clinical dementia over time. Kral and Emery\textsuperscript{19} also reported that patients initially diagnosed as having MDD are more likely to develop dementia during several years. Although published studies\textsuperscript{15,20,21} have found the association between depression and dementia to be relatively weak, the preponderance of evidence supports the assertion that depression can be a risk factor and a prodrome for dementia, especially AD.

The definitive diagnosis of AD requires a history of cognitive decline together with the neuropathologic hallmarks of AD—neuritic plaques and neurofibrillary tangles. Clinical and neuropathologic evidence indicates that the neurobiological changes\textsuperscript{22} underlying AD begin decades before the clinical manifestations of the disorder become apparent.\textsuperscript{23} Braak and Braak\textsuperscript{24} reported that neurofibrillary tangle density increases in some individuals as early as the fourth decade of life, presumably in individuals destined to develop AD over time. Neuritic plaque distribution in the neocortex and limbic regions also can begin decades before AD becomes clinically manifest.\textsuperscript{13}

Positron emission tomography (PET) with specific radioligands has been used to characterize and estimate the in vivo protein load in the brain.\textsuperscript{25-27} 2-[(6-
\[18F\]fluoroethyl)(methyl)amino]-2-naphthylmalononitrile ([\textsuperscript{18F}FDDNP]) is a molecular imaging probe sensitive for the detection of amyloid and tau protein deposition in the brain.\textsuperscript{25,28,29} Binding of [\textsuperscript{18F}FDDNP in vivo correlates well with patterns of amyloid and tau distribution known to exist in AD and determined post mortem.\textsuperscript{25-30} 2-(4-
\[11C\]methylamino)phenyl-6-hydroxybenzothiazole ([\textsuperscript{11C}CIPB]) has been reported to label plaques but not tangles and, like [\textsuperscript{18F}FDDNP, it has the ability to discriminate between patients diagnosed as having AD and controls.\textsuperscript{31} In addition, [\textsuperscript{18F}FDDNP has shown the expected binding progression from mild cognitive impairment (MCI) to dementia that is supported by neuropathologic data in MCI and AD.\textsuperscript{30,32} Binding of [\textsuperscript{18F}FDDNP also is increased in patients diagnosed as having Down syndrome.\textsuperscript{33} Of interest, higher [\textsuperscript{18F}FDDNP binding in the temporal and frontal lobes has been demon-
medical illness, chronic disease such as syphilis that could affect cognitive function, or history or evidence of psychotic symptoms or concurrent Axis I psychiatric disorder. Stable chronic conditions, such as diabetes mellitus, hypertension, or history of cancer, were not exclusionary. All patients received a comprehensive laboratory assessment and a comprehensive neuropsychological battery. Although many of the patients and controls had stable, chronic medical illnesses, none of them had any concurrent brain or psychiatric disorder or any unstable medical illness.

All study participants were screened for dementia based on the clinical evaluation of history, current mental status, and Mini-Mental State Examination score less than 26. Mild cognitive impairment was operationally defined as scoring ~1.5 SDs from the mean on 2 or more tests of verbal or visual delayed recall. One patient with MDD met the criteria for MCI. The tests used for the evaluation included the California Verbal Learning Test—Second Edition, the Rey-Osterrieth Complex Figure test, and the Visual Reproduction subtest of the Wechsler Memory Scale–Third Edition (WMS-III). The California Verbal Learning Test and the Visual Reproduction subtest from the Wechsler Memory Scale were normed according to national samples and the Rey-Osterrieth Complex Figure Design test was normed on the control mean of our large research data bank (N=162 controls). These tests were selected from a comprehensive neuropsychological battery administered to all participants after completion of the imaging phase. The battery included assessment of literacy, explicit verbal learning and recall, explicit nonverbal learning and recall, executive function, attention and processing, implicit learning, and semantic and phonetic language fluency.

METHODS OF PET

The radiofluorinated imaging probe [18F]FDDNP was prepared at high specific activities (>37 GBq/µmol), as described elsewhere.49 All brain scans were performed at the University of California, Los Angeles, Ahmanson Biological Imaging Center with the EXACT HR+ tomograph (Siemens Medical Solutions, Inc, Munich, Germany; and CTI Molecular Imaging Inc, Knoxville, Tennessee), with individuals in the supine position and the imaging plane placed parallel to the orbitomeatal line. After the injection of the positron emission tomographic tracer (320-410 MBq) as a bolus via the indwelling venous catheter, the consecutive dynamic scans via PET were performed for as long as 2 hours. All scans via PET were decay corrected and reconstructed using filtered back-projection (Hann filter, 5.5-mm full width at half maximum) with scatter correction and measured attenuation correction. The resulting images contained 63 contiguous sections with a plane-to-plane separation of 2.42 mm.

QUANTITATIVE ANALYSIS OF DATA FROM IMAGING VIA PET

Image data were analyzed and regions of interest (ROIs) determined, with investigators masked to clinical findings. Quantification of the data regarding [18F]FDDNP binding was performed with the Logan graphic method, with the cerebellum as the reference region for time points between 30 and 125 minutes.45,46 Similar results were obtained when analyses were performed in intervals of between 30 and 60 minutes. The slope of the linear portion of the Logan plot is the relative distribution volume (DVR), which is equal to the distribution volume of the tracer in an ROI divided by the distribution volume of the tracer in the reference region. Early frame [18F]FDDNP images via PET (sum of 0-5 minutes) were oriented in anterior commissure–posterior commissure orientation by rigid coregistration with the SPM2 software package (The MathWorks, Inc, Natick, Massachusetts) to the template for PET provided in the package. The parameters determined in this step were used to orient the [18F]FDDNP DVR images in the same, coregistered, orientation.

A set of ROIs was drawn bilaterally on the frontal, PA, PC, anterior cingulate, mesial temporal, and lateral temporal lobe areas and the cerebellum on each coregistered early frame [18F]FDDNP image via PET separately using the ROI set shown in Figure 1 as a guide. The resulting ROI sets were imported in their corresponding [18F]FDDNP DVR images and DVR values were extracted. Drawing of ROIs and extraction of DVR values were performed using the AMIDE Medical Image Data Examiner software package.48 Each regional DVR or binding value was expressed as the mean of the left and right regions, and global DVR values were calculated as means of the values for all these regions. Rules for ROI drawing were based on the identification of gyral and sulcal landmarks with respect to the atlas of Talairach and Tournoix.47

Brain MRI results were obtained for all study participants with the exception of 2 controls using a 3T scanner (Siemens Medical Solutions, Inc). For each of these individuals, coronal sections that were 1.6-mm thick were obtained (repetition time, 20 milliseconds; echo time, 6 milliseconds; field of vision, 22 cm; 256 × 256 matrix; number of excitations, 1.5; and flip angle, 45°). Axial sections 3-mm thick also were obtained (repetition time, 4000 milliseconds; echo time, 14/112 milliseconds;
field of vision, 24 cm; 256 × 256 matrix; and number of excitations, 1). All MRI results were examined for space-occupying and other focal lesions, including stroke. Patients described in this study were free of overt neuroanatomical abnormalities.

The [18F]FDDNP DVR parametric images of 20 patients with MDD and the 8 controls with available T1-weighted MRI results were coregistered to the T1-weighted MRI results using the transformation parameters determined during the coregistration of [18F]FDDNP images, summed for the first 5 minutes after injection, to the T1-weighted MRI results using statistical parametric mapping (SPM) software. Although 17 of the 19 controls had MRI results, only 8 of them had T1-weighted images that could be used in this analysis. The T1-weighted MRI results and coregistered images via PET were further transformed into the common space using SPM software. The ROIs were drawn on the normalized T1-weighted MRI results bilaterally on the superior and middle frontal gyri on the frontal lobe; the middle temporal gyrus in the lateral temporal lobe; the hippocampus proper, the entorhinal cortex, and the parahippocampal gyrus in the medial temporal lobe; the inferior lobule in the PA lobe; the anterior cingulate gyrus; and the PC gyrus.

The ROI sets were used to extract the DVR values from coregistered [18F]FDDNP parametric images. The DVR values for each brain region are given as the means of the left and right hemisphere DVR values. We imported positron emission tomographic–drawn ROIs into coregistered MRI results and found good matching of ROIs with gray matter areas on MRI results.

### RESULTS

The groups did not differ significantly regarding demographic variables (Table 1). Study participants ranged in age from 60 to 82 years (mean [SD] age, 67.0 [7.2] years) and were well educated (mean [SD] educational level, 16.3 [2.7] years). They showed minimal impairment on cognitive testing (mean [SD] Mini-Mental State Examination score, 29.0 [1.3]; mean [SD] verbal IQ score, 114.6 [10.1]).

The global [18F]FDDNP binding value was significantly higher in our MDD group (n=20) when compared with that of controls (n=19; Table 2). The groups also were significantly different in their regional [18F]FDDNP binding levels, as revealed by the mixed-effects model (F_1,37 = 9.52, \( P = .004 \)). Post hoc t tests demonstrated that the depressed group had significantly higher binding in the lateral temporal and PC regions when compared with controls (Cohen \( d \) effect sizes of 0.92 and 0.67, respectively; Table 2 and Figure 2). Group differences in [18F]FDDNP binding levels in the anterior cingulate and mesial temporal regions approached statistical significance. Figure 3 shows scans of a healthy control individual (low levels of [18F]FDDNP binding) and a patient with MDD (areas of HF, posterior cingulate, and PA binding). In the patient with MDD who met the criteria for MCI, [18F]FDDNP binding values were close to the mean for the MDD group in all regions examined. Furthermore, all findings remained the same when we eliminated this individual from the analyses.

Nonparametric analyses comparing the 20 patients with MDD with the 8 controls (in whom MRI-facilitated [18F]FDDNP–positron emission tomographic analysis was performed) yielded significant group differences in global [18F]FDDNP binding levels (Cohen \( d \) effect size of 1.12, \( P = .03 \)), as well as in PC binding (Cohen \( d \) effect size of 1.07, \( P = .04 \)).

### Table 1. Demographic and Clinical Measures in the Patient and Control Groups

<table>
<thead>
<tr>
<th>Measure</th>
<th>Patients With MDD</th>
<th>Control</th>
<th>Results</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67.45 (8.18)</td>
<td>66.58 (8.27)</td>
<td>.37(^a)</td>
<td>.70</td>
</tr>
<tr>
<td>Sex, No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9</td>
<td>8</td>
<td>.03(^b)</td>
<td>.80</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE score</td>
<td>29.15 (1.14)</td>
<td>28.79 (1.40)</td>
<td>.89(^a)</td>
<td>.40</td>
</tr>
<tr>
<td>Educational level, y</td>
<td>15.73 (2.83)</td>
<td>16.84 (2.46)</td>
<td>-.13(^a)</td>
<td>.20</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>112.55 (10.18)</td>
<td>116.94 (9.73)</td>
<td>-.13(^a)</td>
<td>.20</td>
</tr>
</tbody>
</table>

Abbreviations: ellipses, not applicable; MDD, major depressive disorder; MMSE, Mini-Mental State Examination.

\(^a\) t Test.

\(^b\) \( \chi^2 \) Test.
The key finding of this exploratory study is that patients with late-life MDD demonstrated significantly higher \(^{18}F\)FDDNP binding globally in the cortex with regional accentuation in the lateral temporal and PC regions when compared with healthy controls. Other regions, notably the anterior cingulate and mesial temporal, also showed higher \(^{18}F\)FDDNP binding when compared with controls, although the differences did not reach statistical significance. These findings, along with those of plasma studies of amyloid and \(^{18}F\)FDDNP binding correlates of anxiety and depression symptoms in patients diagnosed as having MCI and cognitively intact elderly individuals, indicate that neuronal injury, secondary to amyloid and tau, may represent a pathophysiologic pathway that, together with vascular compromise, may predispose elderly individuals to mood and related behavioral syndromes and disorders.

This pattern of high \(^{18}F\)FDDNP binding in the PC and lateral temporal regions is the same pattern described in a subgroup of 56 individuals without dementia. The pattern of binding differs from the pattern typically observed in patients diagnosed as having AD in whom \(^{18}F\)FDDNP binding is higher than controls throughout much of the neocortex and more pronounced in mesial temporal and partial regions. In a more recent study, we compared \(^{18}F\)FDDNP binding, with more marked involvement of anterior temporal and mesial regions. In that study, the \(^{18}F\)FDDNP subgroup with high lateral temporal and PC binding demonstrated heterogeneity in its \(^{18}F\)FDG–positron emission tomographic cerebral metabolic patterns in individuals without dementia in 3 subgroups defined according to their \(^{18}F\)FDDNP binding patterns. In the study, the \(^{18}F\)FDDNP subgroup with high lateral temporal and PC binding demonstrated heterogeneity in its \(^{18}F\)FDG–positron emission tomographic patterns, with a predominance of anterior frontal and anterior temporal hypometabolism, consistent with risk of mixed and/or other forms of dementia, including frontotemporal dementia. Our current results suggest that this high lateral temporal and PC binding in patients with MDD can be associated with different clinical patterns: some individuals show a clinical syndrome consistent with MCI but others demonstrate only depression symptoms. Longitudinal follow-up of these patients is necessary to evaluate the significance of these clusters and the clinical outcomes of these patient subgroups.

The control and MDD groups in the current study showed a range of regional \(^{18}F\)FDDNP binding values (Figure 2), suggesting that subgroups of the patients with MDD may show alternative patterns of regional binding, including the \(^{18}F\)FDDNP pattern HF/PA cluster. As shown in a separate study, this \(^{18}F\)FDDNP pattern is associated with an \(^{18}F\)FDG–positron emission tomographic pattern consistent with increased risk of AD (bilateral hypometabolism in the PA, temporal posterior cingulate, and dorsolateral prefrontal regions). Also, longitudinal data of patients with MCI indicate that this HF/PA pattern confers a high risk of cognitive decline after 2 years of follow-up. In these patients with MDD with the HF/PA pattern, depressive symptoms may be the initial manifestations of progressive neurodegenerative disease.

Neuroimaging studies, primarily MRI-based studies, have been used extensively to characterize the neuroanatomical and physiologic changes that underlie late-life MDD. Neuroanatomical approaches have revealed smaller brain volumes in key prefrontal, limbic, and subcortical regions in patients with MDD when compared with controls. Changes in gray matter density identified using sophisticated algorithms have shown increases and decreases when compared with controls. Magnetization transfer–based studies have revealed somewhat diffuse biophysical abnormalities in gray and white matter regions in the brains of patients with MDD. Magnetic resonance imaging–identified high-intensity lesions and abnormalities in fractional anisotropy detected using diffusion tensor imaging also are widespread in patients with MDD. Our current finding of relatively widespread increases in \(^{18}F\)FDDNP binding, with more marked involvement of some regions, is consistent with the findings of earlier neuroimaging studies that indicate that the biological underpinnings of late-life MDD are diffuse and involve multiple regions and neuronal circuits. Our MRI-facilitated positron emission tomographic image analysis of a subgroup also indicated widespread increase in \(^{18}F\)FDDNP binding, although the small sample size precluded regional measures of binding from becoming statistically significant.

The role of amyloid in the pathophysiologic manifestation of depression and dementia has received recent attention, although the findings sometimes are conflicting. Mayeux and coworkers reported that the risk of developing AD increased for individuals with higher plasma levels of Aβ42. Other reports suggest that lower Aβ42/Aβ40 ratios in the plasma identify individuals at risk for dementia, especially AD. Pomara and Murali Dora first proposed that increased platelet activa-

### Table 2. \(^{18}F\)FDDNP Binding Levels by Brain Region and Study Group

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Patients With MDD (n=20)</th>
<th>Control Individuals (n=19)</th>
<th>Patients With MDD vs Controls t Test (df)</th>
<th>P Value</th>
<th>Effect Size Cohen d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>1.10 (0.04)</td>
<td>1.07 (0.03)</td>
<td>2.55 (37)</td>
<td>.01</td>
<td>0.82</td>
</tr>
<tr>
<td>Parietal</td>
<td>1.07 (0.04)</td>
<td>1.05 (0.04)</td>
<td>1.69 (37)</td>
<td>.10</td>
<td>0.54</td>
</tr>
<tr>
<td>Frontal</td>
<td>1.04 (0.06)</td>
<td>1.03 (0.03)</td>
<td>1.13 (37)</td>
<td>.27</td>
<td>0.36</td>
</tr>
<tr>
<td>Posterior cingulate</td>
<td>1.13 (0.04)</td>
<td>1.10 (0.04)</td>
<td>2.09 (37)</td>
<td>.04</td>
<td>0.67</td>
</tr>
<tr>
<td>Anterior cingulate</td>
<td>1.09 (0.05)</td>
<td>1.07 (0.04)</td>
<td>1.96 (37)</td>
<td>.06</td>
<td>0.63</td>
</tr>
<tr>
<td>Mesial temporal</td>
<td>1.11 (0.05)</td>
<td>1.09 (0.04)</td>
<td>1.74 (37)</td>
<td>.09</td>
<td>0.56</td>
</tr>
<tr>
<td>Lateral temporal</td>
<td>1.11 (0.04)</td>
<td>1.07 (0.04)</td>
<td>2.88 (37)</td>
<td>.007</td>
<td>0.92</td>
</tr>
</tbody>
</table>

Abbreviations: \(^{18}F\)FDDNP, 2-((1-β-[[2-\(^{18}F\)fluoroethyl](methyl)-amino]-2-naphthyl(ethylidene) malononitrile; MDD, major depressive disorder.
lation in patients with recurrent depression may lead to higher plasma levels of Aβ that, in turn, contribute to higher brain deposition of amyloid. Plasma studies by Sun and associates in patients diagnosed as having late-life MDD demonstrate that a subgroup of patients have lower levels of Aβ42 and higher Aβ40:Aβ42 ratios. In this study, patients with this plasma profile (high Aβ40:Aβ42 ratio) show impairments in memory and other cognitive domains comparable to the deficits observed in patients with AD. Po- mara and Sidtis reported in their sample of patients with late-life MDD that patients with depression had higher levels of Aβ42 and Aβ42:Aβ40 ratios when compared with controls. Their data also suggest that higher Aβ42:Aβ40 ratios were associated with MRI-related brain abnormalities in patients with MDD. Despite this apparent discrepancy in the literature, both groups of investigators assert that changes in the Aβ42:Aβ40 ratios rather than changes in the absolute levels of either peptide are the relevant peripheral biological marker. These, together with other related observations, have led to the amyloidogenic theory of depression in late life that asserts that in a subgroup of patients with late-life MDD, perturbations of amyloid deposition and biology may be pathophysiologically relevant and may contribute to clinical and/or neuroimaging profiles suggestive of early dementia. Although the plasma results are intriguing, they are peripheral markers of neurobiology and reflect brain activity only indirectly. The precise relationship of plasma levels to brain neuronal levels in disease states and preclinical models has yet to be demonstrated. A study of PET images with validated imaging probes permits a more direct visualization of protein load and amyloid-induced injury in the brain.

An earlier study of PET images using [11C]PIB and a small sample of patients with late-life MDD and controls identified higher [11C]PIB brain retention in patients with MDD compared with controls. Higher [11C]PIB retention was observed in several cortical areas comparable to the distribution seen in patients diagnosed as having AD. Of interest, higher [11C]PIB retention was observed most noticeably in patients with MDD who concurrently met criteria for MCI (amnestic, nonamnestic, and mixed variety). Patients with MDD who did not meet the clinical criteria for MCI had [11C]PIB brain retention parameters comparable to those for controls. In our sample, only 1 of the 20 patients with MDD met the criteria for MCI, and that patient’s [18F]FDDNP binding parameters and distribution were similar to those of other patients with MDD. Our primary findings indicate that in patients with MDD who do not meet the established criteria for MCI, [18F]FDDNP cortical binding is higher than in controls, indicating that brain neuropathologic aggregate deposition is present in MDD even in patients without discernible cognitive impairment.

Depression in late life is clinically and biologically heterogeneous. Current nosologic classifications follow empirical descriptive criteria and a somewhat arbitrary age cutoff for late-life disorders. Comparable to other behavioral and psychiatric classifications, late-life depression is diagnosed exclusively on clinical grounds with no acknowledgment of plausible etiologic considerations. Given this approach, it is not surprising that an entity or entities so defined will be biologically heterogeneous. Studies from sev-
eral laboratories, including ours, have described multiple neuroimaging findings demonstrating several abnormalities in the brains of patients diagnosed as having late-life MDD. These findings include smaller brain volumes, biophysical abnormalities in multiple brain regions, and brain lesions of putative vascular origin. Although it would be premature to include late-life MDD in the category of amyloid and tauopathies, our current findings directly demonstrate that increased neuronal injury also can be correlated (or be secondary) to brain protein deposition, which may constitute another relevant biological mechanism in the underlying biology of MDD. At the cellular level, disparate mechanisms and pathways may converge and synergistically compromise neuronal structure and function even further.

Limitations of the current study include its preliminary nature, relatively small sample size of study groups, and the cross-sectional nature of the design. A longitudinal study with larger study samples is needed to establish the relationship of [18F]FDDNP binding patterns, in vivo, to clinical outcomes. Also, we did not acquire genetic information regarding our patients and control groups. Although the prevalence of the APOE ε4 allele, which is strongly associated with the risk of developing AD, is low in the general population, we are unable to comment on the association, if any, between APOE status and [18F]FDDNP binding in this sample. Also, although we have previously established that [18F]FDDNP binding in AD is predominantly associated with tau aggregate deposition in the medial temporal lobe and largely reflects amyloid aggregates in other cortical areas, it is not possible to more precisely characterize the relative contributions of both of these proteins to [18F]FDDNP binding in vivo.30

In conclusion, this is the first report, to our knowledge, to demonstrate increased [18F]FDDNP binding in focal brain regions suggesting higher amyloid and tau deposition in these brain areas in patients diagnosed as having late-life MDD. The pattern of binding, moreover, differs from that typically seen in patients with AD but it is consistent with that observed in controls at risk for dementia or patients with MCI. Neuronal injury secondary to higher protein deposition may represent a biologically plausible pathway to depression in late life. Longitudinal studies using large clinical samples are needed to determine whether higher [18F]FDDNP binding at baseline leads to AD over time. Also, [18F]FDDNP imaging via PET before and after treatment with conventional antidepressant therapy and antiamyloid agents will provide additional information regarding the change in protein neuropathologic deposition status after successful therapy with biologically relevant agents.

Submitted for Publication: April 27, 2011; final revision received May 31, 2011; accepted June 1, 2011.

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Financial Disclosure: The University of California, Los Angeles, owns US patent No. 6 274 119, titled “Methods for Labeling β-Amyloid Plaques and Neurofibrillary Tangles,” that uses the approach outlined in this article. Drs Small and Barrio are among the inventors of this work, have received royalties for it, and will receive royalties on future sales. Dr Small reports having served as a consultant and/or having received lecture fees from Brainstorming Co; Dakim, Inc; Eisai Co, Ltd; Forest Pharmaceuticals, Inc; Medivation, Inc; Myriad Genetics, Inc; Novartis AG; Ortho-McNeil-Janssen Pharmaceuticals; Pfizer Inc; Radica Games Limited; and Siemens Medical Solutions USA, Inc. Dr Small also reports having received stock options from Dakim, Inc. Dr Barrio reports having served as a consultant for and having received lecture fees from Nihon Medi-Physics Co, Ltd; Bristol-Meyer Squibb; PETNET Solutions; Noscira S.A.; and Siemens Medical Solutions USA, Inc. He also gratefully acknowledges the support of the Elizabeth and Thomas Plott Chair Endowment in Gerontology at the David Geffen School of Medicine at the University of California, Los Angeles.

Funding/Support: This study was supported by National Institutes of Health grants R21MH080258, P01-AG024831, AG13308, P50AG16570, MH/AG58156, MH52453, AG10123, and M01-RR0065; the United States Department of Energy (contract DE-FC03-87-ER0615); the General Clinical Research Centers; the Franc and Ray Stark Foundation Fund for Alzheimer’s Disease Research; the McMahan Family Charitable Foundation; the Ahmanson Foundation; the Parlow-Solomon Professorship at the David Geffen School of Medicine at the University of California, Los Angeles; the Elizabeth and Thomas Plott Chair Endowment in Gerontology; and the Judith Olenick Elgart Fund for Research on Brain Aging. No company provided support of any kind for this study.

Additional Contributions: Emma Rhodes, MA, provided assistance in the final editing and technical assistance in preparation of the manuscript.

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