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Plaque and tangle imaging and cognition in normal aging and Alzheimer's disease

Meredith N. Braskie^{a,b}, Andrea D. Klunder^c, Kiralee M. Hayashi^c, Hillary Protas^{d,h}, Vladimir Kepe^d, Karen J. Miller^e, S.-C. Huang^d, Jorge R. Barrio^d, Linda M. Ercoli^e, Prabha Siddarth^e, Nagichettiar Satyamurthy^d, Jie Liu^d, Arthur W. Toga^c, Susan Y. Bookheimer^{b,e,g}, Gary W. Small^{e,f}, and Paul M. Thompson^{c,*}

^aHelen Wills Neuroscience Institute, University of California Berkeley, CA 94720, USA

^bAhmanson-Lovelace Brain Mapping Center, David Geffen School of Medicine at UCLA, CA 90095, USA

^cLaboratory of Neuro Imaging, Department of Neurology, David Geffen School of Medicine at UCLA, CA 90095, USA

^dDepartment of Molecular and Medical Pharmacology, David Geffen School of Medicine at UCLA, CA 90095, USA

^eDepartment of Psychiatry and Biobehavioral Sciences, David Geffen School of Medicine at UCLA, CA 90095, USA

^fUCLA Center on Aging, CA 90095, USA

^gDepartment of Psychology, David Geffen School of Medicine at UCLA, CA 90095, USA

^hDepartment of Biomathematics, David Geffen School of Medicine at UCLA, CA 90095, USA

Abstract

Amyloid plaques and tau neurofibrillary tangles, the pathological hallmarks of Alzheimer's disease (AD), begin accumulating in the healthy human brain decades before clinical dementia symptoms can be detected. There is great interest in how this pathology spreads in the living brain and its association with cognitive deterioration. Using MRI-derived cortical surface models and four-dimensional animation techniques, we related cognitive ability to positron emission tomography (PET) signal from 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile ([¹⁸F]FDDNP), a molecular imaging probe for plaques and tangles. We examined this relationship at each cortical surface point in 23 older adults (10 cognitively intact, 6 with amnesic mild cognitive impairment, 7 with AD). [¹⁸F]FDDNP-PET signal was highly correlated with cognitive performance, even in cognitively intact subjects. Animations of [¹⁸F]FDDNP signal growth with decreased cognition across all subjects (<http://www.loni.ucla.edu/~thompson/FDDNP/video.html>) mirrored the classic Braak and Braak trajectory in lateral temporal, parietal, and frontal cortices. Regions in which cognitive performance was significantly correlated with [¹⁸F]FDDNP signal include those that deteriorate earliest in AD, suggesting the potential utility of [¹⁸F]FDDNP for early diagnosis.

Keywords

Amyloid; Cerebral cortex; Cognitive aging; Memory; PET

1. Introduction

Decades may elapse between initial cortical accumulations of tau neurofibrillary tangles and amyloid plaques (the major pathologic hallmarks of Alzheimer's disease (AD)) and the cognitive changes required for clinical diagnosis (Braak and Braak, 1991; Thal et al., 2002). Historically, plaques and tangles were only detectable *post mortem*, making the pathological burden difficult to relate to cognitive performance. However, PET probe advances may facilitate investigation of this pathology in living humans. *In vivo* cortical accumulation of the ligand 2-(1-{6-[(2-[F-18]fluoroethyl)(methyl)amino]-2-naphthyl}ethylidene)malononitrile ([¹⁸F]FDDNP) is consistent with depositions of both plaques and tangles in living subjects (Agdeppa et al., 2001b; Small et al., 2006), and previously has been verified via subsequent autopsy to co-localize with plaques and tangles (Agdeppa et al., 2001b). Digital autoradiography of AD brain specimens using [¹⁸F]FDDNP has likewise demonstrated that the pattern of ligand binding matches the pattern of plaques and tangles in neighboring slices (as determined using immunohistochemistry and confocal fluorescence microscopy) (Agdeppa et al., 2001a). Furthermore, in a recent study, global [¹⁸F]FDDNP was shown to be more accurate than FDG-PET or MRI brain volumes at discriminating among clinical diagnoses (Small et al., 2006). In addition to [¹⁸F]FDDNP, PET ligands Pittsburgh Compound B (PIB) (Buckner et al., 2005; Klunk et al., 2004; Mintun et al., 2006) and stilbene (SB-13) (Verhoeff et al., 2004) are both reported to visualize plaques alone. Initial reports have focused on validating the imaging probes and differentiating diagnostic groups by examining signal averaged over regions of interest rather than at each cortical point (Klunk et al., 2004; Small et al., 2006; Verhoeff et al., 2004).

In this study, we compared the voxel-wise spatial relationship between 3D cortical [¹⁸F]FDDNP distribution and cognitive ability across subjects with diagnoses ranging from cognitively intact to mild AD. This approach empowered cortical signal detection without requiring *a priori* specification of regions of interest (ROIs), thus preventing biases that could be introduced by variations in ROI sizes. We evaluated cognition using composite test scores as a continuous measure, which ensured that participants close to diagnostic boundaries did not obscure results as they might with categorical comparisons. Finally, we mapped cortical gray matter thickness (Thompson et al., 2004) both to separate molecular pathology from the effects of structural atrophy and to assess the specificity and independent predictive value of PET versus MRI measures.

2. Methods

2.1. Subjects

Twenty-three community-dwelling subjects were assessed with standard neurological and psychological exams. Those with a history of stroke, mental illness, serious head injury, and non-AD diseases that could affect cognitive performance were excluded. Although subjects were not excluded for presence of white matter lesions, which are frequently present in AD, our composite cognitive test score was not significantly correlated with the occurrence of at least one visible white matter hyperintensity in a T2-weighted MRI image ($p = 0.868$). Seven subjects met diagnostic criteria for AD, 6 for amnesic mild cognitive impairment (MCI) (Petersen, 2004), and 10 were cognitively intact controls, although some had typical age-related memory complaints. Individuals with AD or amnesic MCI were diagnosed

using previously published standard diagnostic criteria (American Psychological Association, 2000; Petersen, 2004). Control subjects did not meet diagnostic criteria for MCI or AD. Diagnostic groups did not differ significantly in age, education, sex, or Hamilton Depression Rating Scale (21 item) (Hamilton, 1960). To maximize the likelihood of finding cognitively intact subjects who have early AD-like pathology, we included several cognitively intact subjects who had a family history of dementia (6), were apolipoprotein E e4 (APOE4) carriers (4), or both (2).

All but seven of the subjects included in the current study also were reported in a study previously published (Small et al., 2006). Subjects from that study who lacked high-quality T1-weighted MPRAGE MRI scans (Siemens 3T) were excluded from our study.

We obtained informed written consent from all subjects or their medical proxies, and the study was approved by the Institutional Review Board of the University of California, Los Angeles (UCLA).

2.2. Neuropsychological testing

Participants underwent a full battery of neuropsychological tests whose scores were converted to age-adjusted Z scores using established age-based normative data for each test. We created a composite average cognitive Z score composed of three tests of episodic memory and three tests of frontal lobe function (Table 1). Selected tasks had a wide range of responses and high sensitivity to AD-related changes (Jones et al., 2006; Tabert et al., 2006) and assessed a range of mental function including memory, processing speed, attentional and response control, and phonemic fluency.

Among the AD patients, cognitive impairment prevented two subjects from completing the Stroop C Interference task, one from completing the Buschke-Fuld Selective Reminding task, and one from completing the WMS Verbal Paired Associates Immediate task. In these cases, we substituted the worst Z score on that task by any study subject for the incomplete test score. No subject failed to complete more than one of the tasks.

Age-adjusted Z scores on the well-established tests performed by subjects were correlated with the composite scores they composed (Pearson's r values range = 0.67–0.90; $p \leq 0.0005$ for all tests), suggesting that the composite score was a valid indicator of memory ability and frontal lobe function in these participants. Averaging Z scores from the individual tests into a composite score reduced the likelihood that an aberrant score on any one task would unduly influence the results of the study. The composite score and the MMSE score were also correlated ($r = 0.73$, $p < 0.0001$). The composite score, however, offered a greater range of values than the MMSE, allowing us to distinguish gradations of cognitive ability even in cognitively intact older adults. A covariance matrix of the age-adjusted Z scores for each test across all subjects showed that all the neuropsychological scores included in the composite score were significantly correlated with one another ($r = 0.42$ – 0.83), suggesting that averaging these scores provided a reasonable single measure of global cognition.

2.3. MRI protocol

We obtained sagittal T1-weighted magnetization prepared rapid acquisition gradient-echo (MPRAGE) volumetric scans (3T Siemens Allegra MRI): repetition time (TR) 2300 ms; echo time (TE) 2.93 ms; 160 slices; slice thickness 1 mm/skip 0.5 mm; in-plane voxel size 1.3 mm $\times$ 1.3 mm; field of view 256 $\times$ 256; flip angle 8°.

2.4. MRI image processing

MRI scans were processed using a sequence of steps described previously (Thompson et al., 2004). We used the Oxford Centre for Functional MRI of the Brain (FMRIB) Software Library (FSL) Brain Extraction Tool (Smith, 2002) and “FSL view” to create and manually refine individual brain masks, which were then applied to exclude non-brain matter. The raw data were scaled and spatially normalized to the International Consortium for Brain Mapping ICBM53 average brain imaging template with a nine-parameter linear transformation (Collins et al., 1994). Magnetic susceptibility artifacts and image non-uniformities were reduced using a regularized tricubic B-spline approach. We automatically segmented each resulting image into gray matter, white matter, and cerebrospinal fluid using a Gaussian mixture model for their MRI signal values (Shattuck et al., 2001).

A three-dimensional cortical surface model was extracted automatically from each subject's scan as described previously (MacDonald et al., 2000). Three-dimensional hemispheric reconstructions were created, onto which a single trained researcher, blind to [^{18}F]FDDNP-PET results, manually traced neuroanatomical landmarks. Inter-rater reliability has been reported previously (Sowell et al., 2000).

We created an inter-subject 3D average cortical model, as detailed previously (Thompson et al., 2003), by flattening the cortex and gyral landmarks into two-dimensional space, then warping all landmarks into alignment across subjects. This method allows voxel by voxel averaging of these images within each delineated region across subjects.

After extracting gray matter volumes (Shattuck et al., 2001) and spatially registering them to the hemispheric models, we calculated cortical gray matter thickness at each point of the brain surface (Sapiro, 2001; Thompson et al., 2004). Our approach defines thickness as the distance from the inner gray—white boundary to the closest point on the outer gray matter surface.

After supersampling the image data to create 0.33 mm isotropic voxels, a 3D Eikonal equation was applied only to gray matter voxels, and a smoothing kernel was used to average gray matter thickness values within a 15-mm sphere at each cortical surface point (Hayashi et al., 2002; Sowell et al., 2004). Test—retest reliability of cortical thickness using repeated scanning and analysis has been reported previously (Sowell et al., 2004).

2.5. [^{18}F]FDDNP-PET scanning

Each subject received a bolus injection of 320–550 MBq [^{18}F]FDDNP, prepared at very high specific activities (>37 GBq/mmol) (Liu et al., 2007), through an in-dwelling venous catheter. Consecutive dynamic PET scans were performed for 2 h on an EXACT HR+ tomograph (Siemens-CTI, Knoxville, TN) while participants lay supine. Sixty-three slices were collected parallel to the orbito-meatal line (2.24 mm plane separation). The scans were decay corrected and reconstructed using filtered back-projection (Hann filter, 5.5 mm FWHM) with correction for scatter and measured attenuation.

2.6. [^{18}F]FDDNP-PET image analysis

We performed Logan graphical analysis (using PET frames 30–125 min) to create distribution volume ratio (DVR) parametric images of relative [^{18}F]FDDNP-PET binding (manifested as PET signal). In these parametric images, the value at each point represented the slope of the linear portion of the Logan plot (or DVR), calculated as the distribution volume of the tracer at that point divided by the distribution volume in the cerebellar reference region (Logan et al., 1996), where little [^{18}F]FDDNP binding was expected.

PET images were co-registered to the MRI images using a mutual information-based rigid body transformation. As described previously (Protas et al., 2005), we assigned PET values to each cortical surface vertex by computing the average value of the DVR image in a kernel of radius 7 mm surrounding each cortical mesh point, while excluding extra-cortical voxels.

For each subject, we also obtained average [^{18}F]FDDNP values within ROIs that included bilateral frontal, parietal, medial temporal, and lateral temporal brain regions as well as posterior cingulate gyrus. These were traced on the co-registered MRI scans as described previously (Small et al., 2006).

2.7. Statistical analysis

Statistical maps were generated indicating the correlation between [^{18}F]FDDNP-PET signal at each cortical surface point and each subject's composite test score. Different statistical models were fitted at each surface vertex, as detailed previously (Thompson et al., 2004), including linear and quadratic terms in the model, and retaining only terms with a significant fit. The resulting significance values associating [^{18}F]FDDNP signal and cognitive performance were indicated by a color code plotted at each surface point on the average cortex. After obtaining average ROI values we additionally performed non-parametric Spearman's rank correlations between regional [^{18}F]FDDNP values and the composite cognitive scores.

2.8. Permutation testing and multiple comparisons correction

The significance map was corrected for multiple comparisons by permutation testing using a threshold of $p < 0.05$ to define a suprathreshold region. The area of this suprathreshold region was compared with a null distribution of statistics that occurred by chance when test scores were randomly assigned to subjects in 100,000 random simulations. Permutation testing has been used widely in imaging and provides a global p value for the observed pattern of effects (Bullmore et al., 1999; Thompson et al., 2003).

2.9. Hypotheses

We used one-sided hypothesis testing, predicting *a priori* that subjects with lower composite scores would show greater [^{18}F]FDDNP signal, particularly in those cortical regions that both degenerate early in Alzheimer's disease and are critical for cognitive performance.

3. Results

3.1. [^{18}F]FDDNP-PET signal and cognitive performance

[^{18}F]FDDNP-PET signal was significantly higher across widespread cortical regions in subjects with poorer neuropsychological test performance (Fig. 1). Strong correlations were seen in the entorhinal, orbitofrontal, and lateral temporal cortices, temporoparietal and perisylvian language areas, parietal association cortices, and much of the dorsolateral prefrontal cortex. Correlated regions were bilateral, except in the medial wall, where above threshold correlations were visible only in the left hemisphere in restricted frontal pole regions, although the difference in signal between hemispheres was not significant. As expected, primary sensorimotor cortices (e.g., central and pre-central gyri) did not show an association between [^{18}F]FDDNP signal variation and cognition.

Notably, cingulate and paralimbic belts did not show detectable correlations on the medial hemispheric surface. However, significant correlations were found in the medial and lateral temporal cortices, where plaques and tangles are thought to be deposited first (Braak and Braak, 1997).

To determine whether these patterns could have been observed by chance, permutation tests were conducted to assign global p values to the maps. At a voxel-level threshold of $p = 0.05$, the corrected significance values were $p = 0.004$ (left hemisphere) and $p = 0.008$ (right hemisphere), suggesting that the results were unlikely to be due to chance.

When only cognitively intact subjects were considered, [^{18}F]FDDNP signal was higher in restricted right frontal cortices, and in some parietal association areas in those having a lower composite cognitive score (Fig. 2). At a voxel-level threshold of $p = 0.05$, the corrected significance value in the right hemisphere was $p = 0.031$ after permutation testing was performed. In the left hemisphere, correlations were detected only in isolated anterior prefrontal regions on the medial wall and in some of the occipital lobe medial surface, but these were not significant after correction for multiple comparisons ($p = 0.129$).

Given that the estimation of a nonlinear model relation was significant both pointwise and overall after permutation testing, it is possible to predict the cortical profile of [^{18}F]FDDNP signal that would be expected at each level of cognitive deterioration. Based on the 65,536 fitted trajectories for [^{18}F]FDDNP signal at the cortical surface vertices across all subjects, we created an image of predicted [^{18}F]FDDNP signal for each composite score value. Maps of mean [^{18}F]FDDNP signal were generated for individuals at each end of the normal range and in the middle of the normal range (maps corresponding to $Z = +2, 0, -2$) (Fig. 3). These Z scores were selected because a person scoring two standard deviations from the mean lies within the 95th percentile for normal performance. Notably, there is a neuroanatomical spread in the areas of higher [^{18}F]FDDNP signal even within the normal range, with greatest signal in the medial temporal, entorhinal, orbitofrontal, and lateral temporal cortices. The increase in frontal [^{18}F]FDDNP signal is characteristic of subjects that are outside the normal range of cognition (see map corresponding to $Z = -4$, or scores 4 standard deviations below the mean). The advancement of pathology can be seen in the accompanying Supplementary Online Data, observable on the internet at <http://www.loni.ucla.edu/~thompson/FDDNP/video.html>.

In this film, frames corresponding to Z scores $+2$ to -4 were estimated from the statistical model fitted at each cortical surface vertex, and were concatenated at 30 frames/s to create a digital animation of the path of pathology with respect to different levels of cognitive performance.

To supplement our cortical surface map results with those obtained using an ROI analysis, we performed Spearman's rank correlations between composite cognitive scores and average [^{18}F]FDDNP signal DVR values in several ROIs: frontal, parietal, medial temporal and lateral temporal regions, and the posterior cingulate gyrus. As hypothesized, when all subjects were included, average [^{18}F]FDDNP values in each region were significantly lower in those having higher composite cognitive scores ($p < 0.05$). Graphs in Fig. 4 demonstrate these relationships in four of the ROIs. In contrast, when only cognitively intact subjects were considered using the ROI analysis (rather than the voxel-wise approach), the composite cognitive score was significantly correlated with average [^{18}F]FDDNP signal only in the posterior cingulate gyrus ($\rho = -0.76$; $p = 0.01$) (not shown). The posterior cingulate gyrus is a region thought to show metabolic changes in subjects at risk for AD (Small et al., 2000).

3.2. Correlations with cortical thickness

In order to determine the independent predictive value of [^{18}F]FDDNP versus MRI-derived measures, we examined the separate relationships of both cognition and [^{18}F]FDDNP signal with cortical thickness. A map of the pointwise relationship between cortical thickness and [^{18}F]FDDNP signal (Fig. 5) showed that such correlations were low and non-significant throughout the cortex. Note that there is no known method to ascribe a global significance

value to a map of correlations between two spatially varying signals, as the exchangeability assumption, required for permutation testing, does not apply, and there is no associated Gaussian field theory yet developed to give such a global p value for two correlated random processes. Interestingly, the pattern of [^{18}F]FDDNP signal in this study did match the pattern of cortical thinning found previously in a population having more advanced AD than the subjects in the current study (Fig. 6B) (Thompson et al., 2003).

Because reduced cortical gray matter thickness has been reported to be associated with AD, MCI, and poorer cognition in prior studies (Apostolova et al., 2006; Singh et al., 2006; Thompson et al., 2004), we also correlated cortical thickness measures with cognitive performance in our sample.

As with [^{18}F]FDDNP signal, cognitive performance was not associated with cortical thickness in this sample (corrected $p > 0.05$; both brain hemispheres).

4. Discussion

Cognitive performance was significantly correlated with [^{18}F]FDDNP signal in right frontal and parietal regions in cognitively intact subjects, suggesting that some cognitive aging that is considered age-normal actually may reflect pathological brain changes, particularly in subjects at risk for AD. That is not to say that plaque and tangle accumulations are a result of aging or are present in all older adults, but rather that in some people diagnosed as having normal cognitive aging, plaques and tangles may be associated with their subtle cognitive decline. Both the lack of significant positive correlations between [^{18}F]FDDNP signal and composite cognitive scores and the rigor of permutation testing supported the validity of our findings.

It is important to note that even though [^{18}F]FDDNP signal was elevated in the medial temporal lobe in some cognitively intact adults, it was primarily in the frontal cortex where [^{18}F]FDDNP signal distinguished those controls who performed better on certain cognitive tasks from those who performed worse. Permutation testing without a restricted *a priori* search region appropriately applies a somewhat conservative correction for false positives, so the correlation in the right hemisphere but not the left may reflect limited statistical power rather than true hemispheric specificity. The specificity of the relationship between [^{18}F]FDDNP signal and cognition for right frontal cortex will be tested specifically in future studies having larger sample sizes.

The correlations we observed in the cognitively intact subjects alone were maintained and expanded when cognitively impaired subjects were also included in the sample. Cognitive performance across all subjects was correlated with [^{18}F]FDDNP signal in inferior and lateral temporal, orbitofrontal, dorsolateral prefrontal, and parietal association cortices—regions with the greatest plaque and tangle burden in histopathological studies of AD (Braak and Braak, 1991). The anatomical agreement is striking between these *in vivo* maps and the well-established *post mortem* maps for the staging of AD (Braak and Braak, 1991).

ROI analyses yielded significant relationships between the composite cognitive scores and the average [^{18}F]FDDNP signal in all regions examined when all subjects were included, but only in the posterior cingulate gyrus when cognitively intact subjects alone were considered. Given the reduced sample size and the restricted range of variability in the [^{18}F]FDDNP signal within the control group, it is not surprising that the controls alone did not demonstrate significant relationships between [^{18}F]FDDNP signal and the composite cognitive score in several of the ROIs. When there is a restricted range of variability in the [^{18}F]FDDNP signal (as there is within the control group), a voxel-wise approach may provide advantages over an ROI approach (in which signal is averaged across significant

and non-significant voxels) for detecting relationships between [^{18}F]FDDNP signal and cognition. It is interesting to note, however, that even using these averaged ROIs to determine [^{18}F]FDDNP signal, the graphs in Fig. 4 demonstrate that there do not appear to be outlying data points in the relationships between [^{18}F]FDDNP signal and composite cognitive scores within the controls, lending support to the significant relationships we found using a voxel-wise statistical mapping approach.

The relationship of plaques and tangles to AD is controversial. Both must accompany specific cognitive impairment for a definitive AD diagnosis (McKhann et al., 1984). Some researchers believe that plaques or tangles cause the disease (Binder et al., 2005; Selkoe, 2001); others contend that these merely tend to co-occur with other more causative disease processes (Castellani et al., 2006; Watson et al., 2005). Neurofibrillary tangle density correlates more strongly with disease severity and neuronal death than does total plaque burden (Berg et al., 1998; Giannakopoulos et al., 2003). However, even in studies in which total plaque load did not correlate with disease severity, a simple comparison of total plaque load in AD subjects versus controls (rather than a correlation with severity of dementia) showed that AD subjects had on average more extensive plaques than controls (Bouras et al., 1994; Gomez-Isla et al., 1996). These data suggest that both plaques and tangles are good indicators of disease processes, regardless of whether they are causative factors in AD. Although we are unable to distinguish [^{18}F]FDDNP signal associated with amyloid plaques from that associated with tau neurofibrillary tangles *in vivo*, a recent study compared [^{18}F]FDDNP-PET scanning and brain autopsy assessment in the same patient (Small et al., 2006). In that study, [^{18}F]FDDNP signal in the medial temporal lobe was mainly associated with tau pathology whereas that in other areas of the brain was overwhelmingly related to amyloid plaque deposition.

We did not find a significant correlation between cortical thickness and either [^{18}F]FDDNP signal or cognition in the current study. However, the significant correlations between [^{18}F]FDDNP signal distribution and cognitive ability in the current study were evident in the same regions that showed cortical thinning related to more advanced AD in our prior studies (Fig. 5B) (Thompson et al., 2003). As such, the pattern of cortical [^{18}F]FDDNP signal in this cognitively intact and mildly affected population very closely matches the topography of cortical thinning known to appear later, albeit with a substantial time-lag. Previous studies that considered cognition and cortical thickness either focused primarily on cognitively impaired subjects or had larger subject samples than we had in the current study (Apostolova et al., 2006; Lerch et al., 2005; Thompson et al., 2004). In contrast, nearly half of the subjects in the current study were normal controls who would not be expected to show anything more than the most subtle pathology-related cortical thinning. This early distribution of plaques and tangles may therefore be followed by MRI-detectable cortical thinning only when neuronal damage has become more extensive than is typically found in cognitively intact older adults. Our results suggest that plaque and tangle deposition occurs early and precedes detectable changes in cortical structure, so [^{18}F]FDDNP may be more sensitive to early cognitive changes than structural MRI measures are, and therefore may offer greater power for disease detection, at least during the early stages of the disease process.

Without partial volume correction, PET measures are influenced by cortical atrophy, which reduces the gray matter volume emitting radioisotope signals, resulting in signal attenuation. However, partial volume correction is arguably less critical for interpretation of [^{18}F]FDDNP-PET scans than for metabolic or perfusion PET images, as the disease tends to elevate [^{18}F]FDDNP signal and reduce cortical thickness. Therefore, any atrophic effect works against finding a disease-associated PET signal increase, and PET increases cannot reasonably be attributed to cortical thinning; use of uncorrected values is, therefore, a

slightly conservative approach. It also avoids the risk of overcorrecting the signal values, which could occur if the partial volume model was not exactly correct, and ensures that any observed [^{18}F]FDDNP signal increase can be interpreted as related to the ligand and not to structural atrophy. Future empirical estimation of partial volume models for different gray/white matter fractions and local cortical geometries may increase the signal-to-noise ratio for detecting correlations with cognition with this ligand, so the current approach should be considered as deliberately conservative.

Eighteen of our 23 subjects were APOE4+, had a known family history of dementia, or both. Because our subjects were at high risk for AD and were highly educated, those who had lower memory ability on certain tasks than their same-age peers were more likely than the general population to be affected by a pathological condition. Including participants from backgrounds representative of the general population in future studies may help to further elucidate these relationships. Finally, the results presented here are cross-sectional; longitudinal follow-up is needed to determine which control subjects will eventually develop AD.

Conflicts of interest

The University of California, Los Angeles, owns a U.S. Patent (6,274,119) entitled “Methods for Labeling Beta-Amyloid Plaques and Neurofibrillary Tangles,” which is licensed to Siemens. Drs. Small, Huang, Satyamurthy, and Barrio are among the inventors and each receives royalties in regard to the application of the FDDNP-PET radioligand. None of the other authors has real or perceived conflicts of interest.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Increasing $[^{18}\text{F}]\text{FDDNP}$ and declining cognition. Cortical maps show that as $[^{18}\text{F}]\text{FDDNP}$ signal (DVR) increased at each cortical surface point (across all subjects), cognitive performance decreased (see Section 2 for calculation of composite test scores). Regions of significant correlation ($p < 0.05$), color-coded in red, follow the profile of tangle and plaque accumulation characteristic of mild AD, as established in large-scale *post mortem* mapping studies (Braak and Braak, 1991). Corresponding maps did not show regions where both $[^{18}\text{F}]\text{FDDNP}$ signal and cognition increased together (not shown here; maps are blue with $p > 0.05$ at all voxels). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Fig. 2. $[^{18}\text{F}]$ FDDNP and cognition in cognitively intact subjects. Frontal regions of the right lateral cortical surface showed elevated $[^{18}\text{F}]$ FDDNP signal in healthy normal subjects with poorer cognitive performance when correlation analyses were restricted to cognitively intact subjects (controls only). Cortical maps show similar correlations between $[^{18}\text{F}]$ FDDNP signal and composite cognitive score as in Fig. 1, but in a more restricted region. Dorsolateral prefrontal regions are implicated in executive function, which is among the functions required for optimal performance on the neuropsychological tests. Additional correlations were found in parietal association areas; the left lateral hemisphere did not show broad regions with correlations (shown on the right panels here). Corroborating these

results, maps of regions in which [^{18}F]FDDNP signal and cognition in cognitively intact subjects increased together showed no effects, as expected (not shown). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Fig. 3. Time-lapse films calibrating maps of $[^{18}\text{F}]$ FDDNP signal versus cognition. Projected mean $[^{18}\text{F}]$ FDDNP signal (DVR) can be calculated for various cognition scores based on the relationship of $[^{18}\text{F}]$ FDDNP signal with cognition in the subjects studied. Here we show projected signal for subjects who scored (A) high normal (2 standard deviations above age-normal), (B) at age-normal levels (Z score = 0), (C) low normal (2 standard deviations lower than age-normal), and (D) at impaired levels (4 standard deviations below age-normal). Red colors denote regions in which greater predicted $[^{18}\text{F}]$ FDDNP signal is associated with lower cognitive Z scores at each cortical point based on a nonlinear spatially varying model. The parameterization of disease stages is based on cross-sectional data, but it is plausible

that a comparable trajectory would be followed for each cognitive stage in an individual subject, albeit with variable timing across individuals. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Fig. 4.

ROI analysis. Scatterplot graphs and linear regressions show the relationship between the composite cognitive scores and average $[^{18}\text{F}]$ FDDNP signal in (A) frontal lobe, (B) parietal lobe, (C) lateral temporal lobe, and (D) posterior cingulate gyrus across all subjects. Average $[^{18}\text{F}]$ FDDNP signal from both hemispheres was pooled for these analyses.

Fig. 5.

PET-MRI correlation. (A) Maps of the pointwise significance between $[^{18}\text{F}]$ FDDNP signal and cortical thickness in millimeters, are shown in 20 subjects. (B) Maps of the pointwise correlation (Pearson's r value) are shown for the same relationship. These maps show that there is no detectable residual correlation between PET and cortical thickness, and therefore the PET effects observed in Figs. 1 and 2 are not confounded by the effects of atrophy. Thickness and PET signal are orthogonal (not correlated) except in very small, scattered regions not overlapping with the main effects in Figs. 1 and 2. The left frontal pole effects cover no more than 5% of the cortex, so they are likely false positives (5% false positives are expected in any null map thresholded at $p = 0.05$).

Fig. 6.

Maps of *post mortem* amyloid load and cortical thickness. (A) Images, which were adapted from Fig. 1 of a previously published paper (Braak and Braak, 1991) (copyright Springer-Verlag, 1991), with kind permission of the authors, Springer Science, and Business Media, display the classic *post mortem* amyloid deposition pattern. Images displayed in (B) also have been previously published (Thompson et al., 2003) (copyright 2003 by the Society for Neuroscience), and show thinner average gray matter in AD patients (mean MMSE = 18) compared with controls at an initial scan (*top right*) and a follow-up scan 1.5 years later, when the mean MMSE for AD patients dropped to 13 (*bottom right*). The pattern of cortical thinning and *post mortem* amyloid deposition displayed previously in patients with mild to moderate AD (upper panels) mirrors those regions demonstrating a significant correlation between cognitive function and [^{18}F]FDDNP signal in Fig. 1 of the current study [adapted with permission from the authors and publishers].

Table 1

Demographics and clinical characteristics.

	AD	MCI	Controls
No. of participants ^a	7	6	10
Average age ^b	77±10.4	73±12.8	73±10.4
Males/females	3/4	2/4	3/7
Years of education ^b	16±2	17±3	17±3
Apolipoprotein E ε4 carriers ^c	4 (57%)	2 (33%)	4 (40%)
Known family history of dementia ^d	2 (29%)	5 (83%)	6 (60%)
Mini-Mental State Exam score ^b	23±2 ^e	28±1 ^e	29±1
Hamilton Depression Rating Scale, 21 item ^b	3±3	4±3	2±2
Cognitive composite Z score ^{b,f}	-2.2±0.9 ^e	-1.0±0.4 ^e	0.7±0.8 ^e

^aTwo participants with AD and one with MCI were excluded from the cortical thickness comparison because of technical difficulties with their MRI scans.

^bListed as mean ± standard deviation.

^cAPOE genotype was not available for two subjects with MCI.

^dFamily history defined as having a parent, grandparent or sibling with dementia.

^eSignificant difference between items indicated.

^fMean age-adjusted Z scores for three tests of verbal memory (Buschke-Fuld Selective Reminding total recall, WMS Logical Memory II delayed total, and WMS verbal paired associates immediate total) and three tests of frontal lobe function (Stroop C interference, WAIS-R digit symbol, and Controlled Oral Word Association Test: FAS).