Brain imaging of cognitively normal individuals with 2 parents affected by late-onset AD

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ABSTRACT

Objectives: This brain imaging study examines whether cognitively normal (NL) individuals with 2 parents affected by late-onset Alzheimer disease (LOAD) show evidence of more extensive Alzheimer disease pathology compared with those who have a single parent affected by LOAD.

Methods: Fifty-two NL individuals received MRI, ^{11}C -Pittsburgh compound B (PiB)-PET, and ^{18}F -fluoro-2-deoxyglucose (FDG)-PET. These included 4 demographically balanced groups ($n = 13/\text{group}$, aged 32–72 years, 60% female, 30% APOE $\epsilon 4$ carriers) of NL individuals with maternal (FHm), paternal (FHp), and maternal and paternal (FHmp) family history of LOAD, and with negative family history (FH–). Statistical parametric mapping, voxel-based morphometry, and z-score mapping were used to compare MRI gray matter volumes (GMVs), partial volume-corrected PiB retention, and FDG metabolism across FH groups and vs FH–.

Results: NL FHmp showed more severe abnormalities in all 3 biomarkers vs the other groups regarding the number of regions affected and magnitude of impairment. PiB retention and hypometabolism were most pronounced in FHmp, intermediate in FHm, and lowest in FHp and FH–. GMV reductions were highest in FHmp and intermediate in FHm and FHp vs FH–. In all FH+ groups, amyloid- β deposition exceeded GMV loss and hypometabolism exceeded GMV loss ($p < 0.001$), while amyloid- β deposition exceeded hypometabolism in FHmp and FHp but not in FHm.

Conclusions: These biomarker findings show a “LOAD parent-dose effect” in NL individuals several years, if not decades, before possible clinical symptoms. *Neurology*® 2014;82:752–760

GLOSSARY

A β = β -amyloid; **AD** = Alzheimer disease; **EOAD** = early-onset Alzheimer disease; **FDG** = ^{18}F -fluoro-2-deoxyglucose; **FH** = family history; **FH–** = negative family history; **FHm** = family history maternal; **FHmp** = family history maternal and paternal; **FHp** = family history paternal; **FWHM** = full width at half maximum; **GM** = gray matter; **GMV** = gray matter volume; **LOAD** = late-onset Alzheimer disease; **MNI** = Montreal Neurological Institute; **NL** = normal; **PiB** = Pittsburgh compound B; **PVC** = partial volume correction (–corrected); **SPM** = statistical parametric mapping; **TIV** = total intracranial volume; **TPM** = tissue probability map; **VBM** = voxel-based morphometry.

Alzheimer disease (AD) is an age-related neurodegenerative disease and the most common form of dementia. Clinical studies indicate that by the time patients seek diagnosis, the amount of irreversible brain damage that may have already occurred hinders treatment potential. Effective interventions, as they become available, ideally would be implemented in at-risk individuals before symptoms occur.

Having a family history (FH) of AD is a major risk factor for developing the disease.^{1,2} While the rare early-onset forms of AD (EOAD) have autosomal dominant genetic inheritance, the risk of developing late-onset AD (LOAD) (i.e., >99% of the AD population older than 60 years) is influenced by genetic and nongenetic factors.¹ Although LOAD does not show recognizable mendelian inheritance, risk is to some extent genetically determined, as shown by the familial aggregation of many cases.² Among probands, those with a parent affected by LOAD are at particularly high risk,^{3,4} and the risk is higher still when both parents are affected.^{5–7} However, because only <5% of individuals have both parents affected by LOAD,^{2,5–7} the clinical profile associated with this rare circumstance has been poorly studied and epidemiologic findings have not been characterized by the use of biomarkers.

Supplemental data at
www.neurology.org

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Many studies indicated that β -amyloid (A β) dysmetabolism is a primary event in the pathogenesis of EOAD.⁸ Fibrillar A β deposition in senile plaques is a cardinal neuropathologic feature in AD and develops many years before clinical symptoms.⁹ However, because many cognitively normal (NL) elderly show A β pathology,¹⁰ its functional significance is unclear. It remains to be established whether A β accumulation is also an early event in LOAD.¹

Previous brain imaging studies have shown that, among NL individuals who have parents with LOAD, those with maternal FH (FHm) present with increased A β load on ¹¹C-Pittsburgh compound B (PiB)-PET,^{11,12} progressive glucose metabolism reductions on ¹⁸F-fluoro-2-deoxyglucose (FDG)-PET,^{13,14} and gray matter volume (GMV) loss on MRI^{15–18} in the same regions as those with clinical AD. In contrast, NL individuals with paternal FH (FHp) are far less likely to show biomarker abnormalities.^{11,13–18}

There are no biomarker studies that examined NL individuals with maternal and paternal FH (FHmp).

The present multimodality brain imaging study used voxel-based techniques such as statistical parametric mapping, voxel-based morphometry (VBM), and *z*-score mapping to simultaneously examine A β deposition, glucose metabolism, and GMV to test whether NL FHmp show more severe biomarker abnormalities than those with one affected parent.

METHODS Subjects. This study included 52 clinically and cognitively NL individuals enrolled in longitudinal studies at New York University School of Medicine. These included individuals interested in research participation and risk consultation and family members and caregivers of patients with AD. Subjects received medical, neuropsychological, and brain imaging examinations within 6 months. Individuals with medical conditions or history of conditions that may affect brain structure or function, i.e., stroke, diabetes, head trauma, any neurodegenerative diseases, depression, hydrocephalus, intracranial mass, and infarcts on MRI, and those taking psychoactive medications were excluded. Subjects were 32 to 72 years of age, with education ≥ 12 years, Clinical Dementia Rating score = 0, Global Deterioration Scale scores ≤ 2 , Mini-Mental State Examination scores ≥ 28 , Modified Hachinski Ischemia Scale scores < 4 , and normal cognitive test performance.^{11,13}

An FH of LOAD that included at least one first-degree relative whose AD onset was after age 60 years was elicited by using standardized questionnaires.^{11,13} The information was confirmed with other family members by interview with the examining physician. Only individuals whose parents' diagnosis of LOAD was reportedly clinician certified and whose parents had lived to age 65 years or older were included. Subjects were divided into 4 demographically balanced groups of 13 subjects each, including FHm, FHp, FHmp, and controls with negative FH of any dementia (FH–). Thirteen FHmp participants completed all procedures. Among the larger pool of participants, we selected 13 FHm, FHp, and FH– subjects who were balanced for demographic characteristics to the FHmp group. Specifically, all of the FHm and FH–, and 11 FHp subjects were individually matched to the FHmp subjects for age (within 3 years), sex, and education. The remaining 2 FHp subjects were matched to the FHmp group for their mean age and educational level (table 1). The AD-affected parents of 4 subjects (1 FHmp, 2 FHm, and 1 FHp) received the postmortem diagnosis of AD.

Standard protocol approvals, registrations, and patient consents. All subjects signed informed consent to participate in this institutional review board–approved study.

Brain imaging. All subjects received volumetric 1.5-tesla MRI (124-slice, T1-weighted, fast gradient echo, 1.2-mm sections, no interslice gaps), PiB-PET, and FDG-PET scans following standardized procedures.^{11–14,16} For PET, subjects were positioned in the scanner 60 minutes postinjection of 15 mCi of ¹¹C-PiB, and scanned for 30 minutes in 3-dimensional mode on an LS Discovery or BioGraph PET/CT scanner.¹² The FDG scan was performed 30 minutes after completion of the PiB scan or on a separate day. After an overnight fast, subjects were injected with 5 mCi of FDG, positioned in the scanner 35 minutes postinjection, and scanned for 20 minutes. All images were corrected for photon attenuation, scatter, and radioactive decay and smoothed for uniform resolution.¹⁹

Table 1 Clinical and neuropsychological measures by FH group

	FH–	FHp	FHm	FHmp
No.	13	13	13	13
Age, y	56 (11)	56 (11)	56 (12)	56 (12)
Sex, M/F	5/8	6/7	5/8	5/8
Education, y	17 (2)	17 (2)	17 (2)	17 (2)
APOE $\epsilon 4$ carriers/noncarriers	4/9	5/8	6/7	4/9
APOE $\epsilon 4/\epsilon 4$	2	1	1	1
APOE $\epsilon 3/\epsilon 4$	2	4	5	3
APOE $\epsilon 3/\epsilon 3$	6	8	6	8
APOE $\epsilon 2/\epsilon 3$	3	0	1	1
Affected parent's age at onset, y				
Mother	NA	NA	72 (10)	76 (7)
Father	NA	78 (7)	NA	80 (9)
Mini-Mental State Examination score	29.5 (0.9)	29.4 (0.9)	29.7 (0.5)	29.5 (0.5)
Digit symbol substitution	59 (12)	58 (11)	58 (11)	62 (11)
Designs	7 (2)	6 (2)	8 (2)	8 (2)
Object naming	28 (2)	28 (1)	28 (1)	29 (2)
Paired associates, delayed recall	10 (3)	10 (3)	10 (3)	11 (3)
Paragraph delayed recall	6 (3)	6 (2)	6 (2)	7 (3)
Gray matter volume, dm ³	0.72 (0.06)	0.71 (0.05)	0.71 (0.07)	0.69 (0.06) ^a
White matter volume, dm ³	0.51 (0.03)	0.51 (0.03)	0.50 (0.04)	0.50 (0.05)
CSF volume, dm ³	0.33 (0.04)	0.31 (0.02)	0.31 (0.04)	0.31 (0.04)

Abbreviations: FH = family history of late-onset Alzheimer disease; FH– = negative FH; FHm = FH maternal; FHmp = FH maternal and paternal; FHp = FH paternal; NA = not applicable.

Data are mean (SD) or count.

^aDifferent from FH–, *p* < 0.05.

For each subject, summed PET images corresponding to 40 to 60 minutes of FDG data and 60 to 90 minutes of PiB data were coregistered to MRI using the normalized mutual information routine of statistical parametric mapping (SPM8).²⁰ Parametric standardized uptake value ratio images were generated by normalizing PiB uptake by cerebellar gray matter (GM) uptake²¹ and FDG by pons activity.²² MRIs were segmented into GM, white matter, and CSF and normalized to Montreal Neurological Institute (MNI) space by high-dimensional warping (DARTel) using VBM8.²⁰ PET scans were corrected for partial volume (PVC) effects.²³ MRI-coregistered raw and PVC FDG and PiB scans were spatially normalized using subject-specific transformation matrixes obtained from MRI, and smoothed with a 10-mm full width at half maximum (FWHM) filter.

MRIs were examined using VBM.^{20,24} A custom template was created using MRI from all subjects by normalizing and segmenting the MRIs using the unified segmentation model with the MNI template and tissue probability maps (TPMs), and averaging the normalized subject TPMs. Individual scans were then processed using the custom TPMs. Jacobian modulation was applied to restore absolute GMVs in the GM images, which were smoothed with an 8-mm FWHM kernel. Total GM, white matter, CSF, and intracranial volumes (TIV) were calculated.

Statistical analysis. SPSS version 19 (IBM Corp., Armonk, NY) and SPM8 were used for analysis. Clinical and demographic measures were examined with the general linear model and χ^2 tests. A full factorial model with post hoc linear t -contrasts was used to test for regional differences in GMV, raw and PVC PiB and FDG across groups. We first compared the combined FHmp, FHm, and FHp groups (FH+) vs FH−, and then tested for differences across FH+ groups and vs FH−. No proportional scaling was performed because PET scans were normalized to reference regions, and GMV images were corrected for TIV. Including TIV as a covariate left results substantially unchanged. Age and *APOE* genotype were examined as covariates. Analyses were repeated in a subset of subjects aged 60 years or younger.

Spatially normalized MRI and PVC PiB and FDG images were used to create z -score maps for each subject against controls, to directly compare the degree of A β load, hypometabolism, and GMV loss.²⁵ The z -score maps were examined with paired t tests across all subjects and within groups.

Because we had specific a priori hypotheses on which brain regions would show possible biomarker effects, results were examined at $p < 0.001$, uncorrected (cluster extent ≥ 20 voxels, i.e., ≥ 2 times the FWHM),²⁰ in the search volume defined by a masking image created from a set of predefined AD-related regions of interest (posterior cingulate cortex/precuneus [BA 23/31/7], inferior and superior parietal lobule [BA 40/39], medial and lateral temporal cortex [BA 21/22/37/38, including hippocampus], medial and prefrontal cortex [BA 8/9/10], and striatum).^{11–14,16} Anatomical location of brain regions showing significant effects was described using Talairach and Tournoux coordinates, after conversion from MNI space.

RESULTS Clinical characteristics of the subjects under study are found in table 1. There were no group differences in clinical and neuropsychological measures, *APOE* status, and age at onset of the affected parents (table 1).

On MRI, the FHmp group showed reduced GMV in temporal cortex and striatum compared with FH− and FHm groups, and in parietal and frontal regions compared with FHp and FHm groups ($p < 0.001$; figure 1, table e-1 on the *Neurology*[®] Web site at www.neurology.org). Both FHm and FHp groups

showed reduced GMV in precuneus compared with FH−, and the FHm group showed additional GMV reductions in parietal cortex vs FHp ($p < 0.001$; figure 1, table e-1). Overall, GMV reductions were most pronounced in FHmp and intermediate in FHm and FHp vs controls (figure 2). Analysis of whole-brain volumes extracted from VBM confirmed that FHmp had reduced GMV compared with FH− ($p < 0.05$), while there were no significant differences for FHm and FHp (table 1).

On PiB-PET, before and after PVC, the FHmp group showed increased PiB retention in frontal and parietal regions and striatum compared with FH− and FHp groups ($p < 0.001$; figure 1, table e-2). PiB accumulation tended to be more severe than in FHm in regard to the number of regions affected and magnitude of impairment (figures 1 and 2, table e-2), although the effect was marginally significant ($p \leq 0.01$). The FHm group showed increased PiB retention in frontal regions compared with FH− and FHp, and in additional temporal regions compared with FHp ($p < 0.001$; figure 1, table e-2). Overall, PiB retention was highest in FHmp, intermediate in FHm, and lowest in FHp and controls (figures 1 and 2).

On FDG-PET, both FHmp and FHm groups showed reduced FDG uptake in posterior cingulate, precuneus, and temporal regions compared with FH−, and in frontal regions compared with FHp ($p < 0.001$; figure 1, table e-3). Hypometabolism was more extended in FHmp than in FHm (figure 1). Metabolic reductions in FHmp vs the other groups remained significant after PVC, as did frontal hypometabolism in FHmp and FHm vs FHp ($p < 0.001$). Overall, FDG uptake was lowest in FHmp, intermediate in FHm, and highest in FHp and controls (figure 2).

For all analyses, no brain regions showed biomarker abnormalities in FHp or FH− vs the other groups, or in FHm and FHp vs FHmp. For all modalities, results remained substantially unchanged accounting for age and *APOE* status.

Analysis was repeated in the 36 NL individuals aged 60 years or younger, including 9 subjects per group who were matched by age (in all groups, mean age = 50 ± 7 years), sex (6 women), and education (17 ± 2 years), and there were 4 *APOE* $\epsilon 4$ carriers in each group. Results were substantially unchanged from those in the entire group, with FHmp subjects showing the most severe abnormalities ($p < 0.001$; figure 3).

On paired t tests of z -score images, there were no regions showing evidence of one biomarker abnormality exceeding that of the others in the FH− control group. Across all FH+ subjects, the extent of PiB load exceeded that of GMV reductions in medial and orbitofrontal cortex and parietotemporal regions, and exceeded that of FDG hypometabolism in medial frontal cortex,

Figure 1 Statistical parametric maps showing brain imaging abnormalities in each family history (FH) group compared with controls

(A) Reduced gray matter volume, (B) higher Pittsburgh compound B (PiB) retention, (C) reduced ^{18}F -fluoro-2-deoxyglucose (FDG) uptake. Statistical parametric maps are represented on different color-coded scales ($1 < z < 3$; $z > 2$ correspond to $p < 0.001$) and displayed onto a standardized MRI. FH- = negative FH; FHm = FH maternal; FHmp = FH maternal and paternal; FHp = FH paternal.

Figure 2 MRI gray matter volume, PiB retention, and FDG metabolism extracted from the clusters showing maximal statistical differences in normal FHmp (black circles), FHm (gray circles), and FHp (white circles) vs FH− (diamonds)

PiB and FDG measures are partial volume-corrected values (i.e., cortical-to-cerebellar PiB and cortical-to-pons FDG standardized uptake value ratio per gram of brain tissue). Boxplots show means, SEM, and SD. FDG = ^{18}F -fluoro-2-deoxyglucose; FH = family history; FH− = negative FH; FHm = FH maternal; FHmp = FH maternal and paternal; FHp = FH paternal; PiB = Pittsburgh compound B; PVC = partial volume-corrected.

inferior temporal areas, precuneus, and striatum ($p < 0.001$; figure 4). Hypometabolism exceeded GMV reductions in parietotemporal and lateral frontal cortices, and exceeded PiB retention in some smaller clusters located in parietotemporal regions. GMV reductions exceeded hypometabolism in left caudate ($p < 0.001$; figure 4). There were no brain regions in which the extent of GMV reductions exceeded that of PiB retention. Overall, PiB abnormalities exceeded those of the other biomarkers in magnitude and in size (figure 4). Specifically within each FH group, pattern results were essentially indistinguishable from the entire sample, with the exception that in the FHm group there were no regions in which the extent of PiB retention exceeded that of hypometabolism ($p < 0.001$; figure 4).

DISCUSSION There is a paucity of studies in FHmp. The few published epidemiologic studies showed that children of 2 parents affected by LOAD have higher lifetime risk of AD than NL individuals with one affected parent or no affected parents,^{5–7} by virtue of carrying a higher burden of yet unknown biological risk factors. However, these studies compared FHmp either with FH− or with a combined group of individuals with one AD parent, neglecting possible risk differences between maternal and paternal transmission.^{5–7} Our results provide biological evidence for the hypothesized “parent-dose effect” on LOAD risk by showing a novel association between established AD biomarkers and a double parental history of LOAD. NL FHmp presented with co-occurring increased A β burden, hypometabolism, and GMV loss in the same brain regions as in clinical AD,¹⁰ which were more pronounced vs NL with one LOAD parent and vs controls regarding the number of regions affected and magnitude of impairment.

Additionally, there were significant parent-sex effects. NL FHmp showed the highest degree of biomarker abnormalities, followed by NL FHm at intermediate levels of pathology, while FHp showed the lowest degree of impairment. Thus, FHmp status confers the highest amount of presumed risk, but FHm status also confers greater risk to the offspring than FHp status. These data are consistent with epidemiologic and biomarker findings that maternal transmission is associated with higher risk than paternal transmission, independent of increased female longevity.^{2,11,13–18,26–31} Present findings expand on prior unimodality biomarker studies showing multiple biomarker deficits in NL FHm, which appeared to be overall less severe than in FHmp. Interestingly, NL FHm was the only group in which A β load did not significantly exceed hypometabolism. While this could be attributable to the small sample, it is possible that other mechanisms, such as maternally transmitted mitochondria bioenergetics deficits, may account for this finding.²

Figure 3 Statistical parametric maps showing brain imaging abnormalities in normal individuals aged 60 years or younger in each family history (FH) group compared with controls

(A) Reduced gray matter volume, (B) higher PiB retention, (C) reduced FDG uptake. Statistical parametric maps are represented on different color-coded scales ($1 \leq z \leq 3$; $z \geq 2$ correspond to $p \leq 0.001$) and displayed onto a standardized MRI. FDG = ^{18}F -fluoro-2-deoxyglucose; FH- = negative FH; FHm = FH maternal; FHmp = FH maternal and paternal; FHp = FH paternal; PiB = Pittsburgh compound B.

(A) PiB vs MRI. (A.1) The degree of A β load exceeds that of GMV loss; (A.2) the degree of GMV loss exceeds that of A β load (not significant). (B) PiB vs FDG. (B.1) The degree of A β load exceeds that of hypometabolism; (B.2) the degree of hypometabolism exceeds that of A β load. (C) FDG vs MRI. (C.1) The degree of hypometabolism exceeds that of GMV loss; (C.2) the degree of GMV loss exceeds that of hypometabolism. (D) Contrasting the extent of biomarker abnormalities in FHmp, FHm, and FHp subgroups. Statistical parametric maps are represented on different color-coded scales ($1 \leq z \leq 5$) and superimposed onto a standardized MRI. A β = β -amyloid; FDG = 18 F-fluoro-2-deoxyglucose; FH = family history; FH+ = positive FH; Hm = FH maternal; FHmp = FH maternal and paternal; FHp = FH paternal; GMV = gray matter volume; PiB = Pittsburgh compound B.

The neuropathologic changes of AD are known to precede the clinical expression of disease by many years.⁸ The presence of altered biomarkers in relatively young NL FHmp, and to a lesser extent FHm and FHp, suggests that these brain abnormalities had begun at even younger ages. The degree and extent of A β load exceeded that of the other biomarkers, suggesting that A β pathology may, at least in part, account for FDG and MRI deficits in NL FHmp. PiB-PET abnormalities are known to be predictive of future AD.^{32–34} However, present cross-sectional results do not offer information on the temporal order in which biomarker alterations occur or on how one biomarker influences the other.

Longitudinal follow-up studies and larger samples are necessary to determine whether the observed biomarker abnormalities are predictive of future dementia, and according to parental dose.

PiB-PET studies of presymptomatic EOAD have shown that A β accumulates early in the striatum of mutation carriers, and to a lesser extent in neocortex.³⁵ A β deposition in our NL FH+ was more prominent in cortical than subcortical regions, supporting the idea of different A β deposition patterns in EOAD and LOAD.^{8,35}

Previous PET studies showed altered AD biomarkers in NL carriers of the *APOE* $\epsilon 4$ allele, a major LOAD

genetic risk factor.^{36,37} *APOE* allelic variations occur in all individuals, and genotypes can be established at any age. In comparison, NL FHmp do not exist in great numbers because this rare condition occurs in <5% of individuals.^{2,5–7} Moreover, it is particularly challenging to find young FHmp because the parents also need to be old enough to have developed dementia. To our knowledge, there are no prior imaging studies that were able to recruit such a cohort. Despite a smaller sample, we were able to show clear biomarker differences across groups, and also to recruit a sufficient number of subjects to repeat the analysis in a subset of 36 NL individuals aged 60 years or younger, which showed that the younger FHmp still had higher A β burden than the other groups. Results were independent of *APOE* genotype, and only 30% of our subjects were $\epsilon 4$ carriers. Unfortunately, the small sample precludes analysis of interactions between FH and *APOE* genotypes. Descriptively, *APOE* genotypes did not seem to be the main determinants of biomarker abnormalities by FH group (figure e-1). The FHmp group showed more severe biomarker abnormalities vs other groups despite including slightly more *APOE* $\epsilon 3/\epsilon 2$ carriers, who presumably carry lower risk of AD.¹ FHmp included 2 $\epsilon 4/\epsilon 4$ and 2 $\epsilon 3/\epsilon 4$ carriers, while FHm and FHp groups both included one $\epsilon 4/\epsilon 4$ but 1 or 2 additional $\epsilon 3/\epsilon 4$ carriers (table 1). As such, it is not possible to make inferences about the contribution of different *APOE* genotypes to current results. Additionally, the *APOE* $\epsilon 4$ genotype has been associated with an earlier age at onset of AD,¹ whereas the age at onset of the AD parents was comparable across groups, further indicating lack of substantial *APOE*-related effects in our cohort. However, we do not have information on the parents' *APOE* genotypes. Because a clear relationship was shown among age, *APOE*, and A β deposition,³⁸ studies with larger samples are needed to determine how each genotype relates to AD biomarkers in combination with FH, as well as in probands and their parents.

Steps were taken to ensure that the AD diagnosis in the subjects' parents was accurate. An FH of LOAD was elicited using standardized questionnaires that are known to have good agreement with neuropathologic findings.³⁹ Nonetheless, our cohort may have included subjects whose parents did not have AD but another dementia. This would lead to inclusion of subjects with lower risk of AD in the FH+ groups, conservatively reducing power in detecting group differences. While we only included subjects whose parents had lived to age 65 years or older, our cohort may have included subjects whose parents had passed away before developing dementia or any *APOE*-related features. However, this would lead to inclusion of subjects with higher risk of AD among controls, or to including an FHmp subject in the FHm or FHp group, also reducing power to detect group differences.

We caution that the NL population selected in our study represents a group with a high a priori risk of preclinical AD changes, and results were made with small numbers of carefully screened subjects under controlled clinical conditions. Replication of these preliminary research findings in community-based populations is warranted and clinical application is not justified.

AUTHOR CONTRIBUTIONS

Dr. Mosconi: study concept and design, acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content, study supervision. Mr. Murray, Dr. Tsui, Dr. Li, Ms. Spector, and Mr. Goldowsky: acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content. Ms. Williams: acquisition of data, analysis and interpretation, study supervision. Dr. Osorio: acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. McHugh: study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content. Dr. Glodzik: study concept and design, analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. Vallabhajosula: acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content. Dr. de Leon: study concept and design, analysis and interpretation, critical revision of the manuscript for important intellectual content.

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DISCLOSURE

L. Mosconi has a patent on a technology that was licensed to Abiant Inc. by NYU and, as such, has a financial interest in this license agreement and holds stock and stock options on the company. Dr. Mosconi has received compensation for consulting services from Abiant Inc. J. Murray reports no disclosures. W. Tsui has a patent on a technology that was licensed to Abiant Inc. by NYU and, as such, has a financial interest in this license agreement and holds stock and stock options on the company. Y. Li has received compensation for consulting services from Abiant Inc. N. Spector, A. Goldowsky, S. Williams, and R. Osorio report no disclosures. P. McHugh was principal investigator (PI) on an investigator-initiated clinical trial supported by Bayer Healthcare Pharmaceuticals. L. Glodzik has received honoraria from the French Alzheimer's Foundation and was PI on an investigator-initiated clinical trial supported by Forest Labs. S. Vallabhajosula reports no disclosures. M. de Leon has a patent on a technology that was licensed to Abiant Inc. by NYU and, as such, has a financial interest in this license agreement and holds stock and stock options on the company. Dr. de Leon has received compensation for consulting services from Abiant Inc., has received honoraria from the French Alzheimer's Foundation, and was PI on an investigator-initiated clinical trial supported by Neuroptix. Go to Neurology.org for full disclosures.

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