Association of hypometabolism and amyloid levels in aging, normal subjects

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ABSTRACT

Objective: We evaluated the relationship of amyloid, seen on Pittsburgh compound B (PiB)-PET, and metabolism, seen on [18F]-fluorodeoxyglucose (FDG)-PET, in normal subjects to better understand pathogenesis and biomarker selection in presymptomatic subjects.

Methods: Normal participants (aged 70–95 years; 600 with PiB-PET, FDG-PET, and MRI) were included. We performed a cross-sectional evaluation and subcategorized participants into amyloid-negative (<1.4), high-normal (1.4–1.5), positive (1.5–2.0), and markedly positive (>2.0) PiB standardized uptake value ratio groups representing different levels of amyloid brain load. Associations with metabolism were assessed in each group. Relationships with *APOE* ε4 carriage were evaluated.

Results: Hypometabolism in "Alzheimer disease (AD)-signature" regions was strongly associated with PiB load. Hypometabolism was greater with more positive PiB levels. Additional, more-diffuse cortical hypometabolism was also found to be associated with PiB, although less so. No hypermetabolism was seen in any subset. No significant incremental hypometabolism was seen in *APOE*-positive vs -negative subjects.

Conclusions: Hypometabolism in PiB-positive, cognitively normal subjects in a population-based cohort occurs in AD-signature cortical regions and to a lesser extent in other cortical regions. It is more pronounced with higher amyloid load and supports a dose-dependent association. The effect of *APOE* ε4 carriage in this group of subjects does not appear to modify their hypometabolic "AD-like" neurodegeneration. Consideration of hypometabolism associated with amyloid load may aid trials of AD drug therapy. *Neurology*® 2014;82:1959–1967

GLOSSARY

AD = Alzheimer disease; **CN** = cognitively normal; **FDG** = [18F]-fluorodeoxyglucose; **FDR** = false discovery rate; **PiB** = Pittsburgh compound B; **ROI** = region of interest; **SUVR** = standardized uptake value ratio.

Hypothetical models of the temporal sequence of brain-imaging biomarker findings that may reflect the Alzheimer disease (AD) pathologic cascade have been proposed by our group and others.[1–4] Understanding the relationship of biomarker abnormalities at their earliest stages will help explain the pathologic mechanisms of AD, aid in targeted therapy approaches, and aid in determining the utility of biomarkers in patients with preclinical AD pathology and in patients with early dementia.

Most reports to date have only considered the relationship of amyloid-positive vs -negative normal subjects and hypometabolism. This does little to elucidate the effect of different levels of amyloid on brain metabolism in presymptomatic subjects. To further elucidate the association between amyloid load and metabolism, we cross-sectionally examined a very large group of cognitively normal (CN) elderly subjects.

METHODS **Standard protocol approvals, registrations, and patient consents.** Participants were drawn from the Mayo Clinic Study of Aging as described previously.[3] [18F]-fluorodeoxyglucose (FDG)-PET and Pittsburgh compound B (PiB)-PET were performed on the same day. All participants provided written consent with approval of the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. MRI scans were performed a median of 16 days before the PET scans. A total of 606 Mayo Clinic Study of

Aging participants considered CN based on a consensus diagnosis after thorough clinical and cognitive assessment by neurologists, geriatricians, neuropsychologists, and study nurses[5] completed the above imaging between December 8, 2004 and September 2012, and were available for analysis. Six subjects were excluded because of imaging/*APOE*-quality issues (3) or brain lesions (3). Our consensus diagnostic process uses quantitative data from a brief mental status examination, 9 neuropsychological tests, and the Clinical Dementia Rating scale, but uses a consensus approach rather than rigid adherence to cut-scores to arrive at a diagnosis of CN.[5]

PET imaging methods. MRIs were performed at 3 tesla using an 8-channel phased array coil (GE, Milwaukee, WI). Image acquisition and image analysis are described in detail elsewhere.[6] PiB-PET global cortical uptake normalized to cerebellar gray matter (standardized uptake value ratio [SUVR]) was then used to assign subjects to groups of different levels of PiB uptake. FDG-PET cortical-to-pons ratios were calculated for each brain region (SUVR). No partial volume correction was used. Subjects were classified according to PiB SUVR into 4 groups: amyloid-negative (<1.4), high-normal (1.4–1.5), positive (1.5–2.0), and markedly positive (>2.0) (table 1).

Statistical analysis. In our first analysis, which was performed separately for each of 47 regions of interest (ROIs), we used linear regression to examine the association between regional FDG and global PiB after adjusting for age and sex. We summarize these results by showing the mean FDG within each of the 4 PiB groups. In addition, we report a false discovery rate (FDR)-corrected p value of a "dose-effect" test of the association between regional FDG and the logarithm of PiB after accounting for age and sex. The logarithm transformation was used to reduce skewness and prevent subjects with the highest levels of PiB from having an outsized influence on the model fit.

We followed this analysis with a very similar regression analysis, looking at differences in regional FDG by *APOE* ε4 carrier status after accounting for age, sex, and PiB. We report 2 sets of uncorrected p values for this analysis. The first set of p values is from a test of *APOE* ε4 carrier status with age and sex in the model, but not PiB. The second set of p values is from a test of *APOE* with age, sex, and PiB in the regression model.

In a third analysis, we examined the association between regional FDG and regional PiB after accounting for age and sex. Because the subject groupings based on cortical PiB were not applicable at the regional PiB level, for each ROI we defined a PiB group based on tertiles for that region. Here, we are able to report a dose-effect test of the association between regional FDG and the logarithm of regional PiB after accounting for age and sex.

In a final set of analyses, we used multivariable logistic regression to identify a parsimonious subset of regions that provide independent information for predicting association of elevated PiB, defined here as PiB >1.5. With 47 regions under consideration, we wanted to protect against overfitting, which is dependent on the number of variables considered rather than the number of variables in a final model. We therefore used penalized logistic regression to shrink coefficients toward the null and thus account for possible overfitting.[7] The method of penalization we used is named the "elasticnet" and is a combination of a penalty based on the sum of squares of the coefficients (as in ridge regression) and the sum of absolute values of the coefficients (as in the lasso).[8] We used version 1.9-1 of the glmnet package in R version 2.15.2 (http://www.-R-project.org) and set the elasticnet mixing parameter to 0.8 so that the lasso penalty was predominant but there remained a degree of ridge regression. In our analyses, age and sex were included in the model but not penalized. This was done by treating age as a continuous variable and indicating in the glmnet software that the age and sex coefficients should be excluded from any penalization. We used leave-one-out cross-validation to select a parsimonious model using the "1-SE rule" in which the final model has cross-validation error within 1 standard error of the optimal model.

To compare the relative strength of associations between "AD-signature" regions and "non–AD-signature" regions and amyloid load, we averaged the FDG uptake in the angular gyrus and posterior cingulum regions and evaluated whether FDG hypometabolism in this composite AD-signature region was more strongly associated with global PiB than the FDG hypometabolism in several non–AD-signature regions (8 frontal regions; superior, middle, superior orbital, middle orbital, inferior orbital, medial superior, and supplementary motor). To do this, we performed a formal test of dependent overlapping correlations.[9] We next averaged the regional PiB levels in this composite AD-signature region and compared the strength of associations between the composite FDG hypometabolism and composite

Table 1	Patient characteristics				
	PiB group				
Characteristic	**<1.4**	**1.4-1.5**	**1.5-2.0**	**>2.0**	**p**
No. of subjects	340	73	117	70	
Males, n (%)	185 (54)	40 (55)	66 (56)	38 (54)	0.99[a]
Age, y	77 (74, 82)	78 (74, 84)	80 (76, 83)	80 (76, 83)	<0.001[b]
Education level, y	14 (12, 16)	14 (12, 16)	14 (12, 16)	14 (13, 16)	0.51[b]
MMSE score	28 (28, 29)	28 (27, 29)	28 (27, 29)	28 (27, 29)	<0.001[b]
CDR-SB >0, n (%)	15 (4)	2 (3)	6 (5)	14 (20)	<0.001[a]
APOE ε4 carrier, n (%)	53 (16)	17 (23)	49 (42)	29 (41)	<0.001[a]
Global cognition composite z score	0.8 (0.2, 1.4)	0.8 (0.1, 1.1)	0.6 (−0.0, 1.2)	0.3 (−0.2, 0.7)	<0.001[b]

Abbreviations: CDR-SB = Clinical Dementia Rating–Sum of Boxes; MMSE = Mini-Mental State Examination; PiB = Pittsburgh compound B.
Values are median (interquartile range) unless otherwise indicated.
[a] Based on χ^2 test comparing groups.
[b] Based on Spearman rank correlation test.

PiB uptake vs regional FDG and regional PiB in the non-AD regions using a test of dependent nonoverlapping correlations.[10] To account for age and sex, we regressed these factors out of the PiB measures before performing our correlation analyses.

RESULTS Table 1 summarizes the clinical characteristics of a sample of 600 CN subjects and indicates that higher PiB was associated with increasing age, worse cognitive performance, and *APOE* ε4 carrier state.

Hypometabolism was associated with global PiB on ROI analysis (figure 1). The strongest associations were seen in regions that are typical AD-signature regions (angular gyrus, posterior cingulate, temporal and parietal regions). Associations were seen in many other regions with decreasing significance.

Regarding *APOE*, FDG was generally not lower among *APOE* ε4 carriers compared with noncarriers after accounting for PiB level. A hypothesis-generating minor exception was the posterior cingulum, in which carriers tended to average lower FDG by approximately 0.03 SUVR units. After adjusting for PiB, they had a $p = 0.04$ without FDR correction. With FDR correction, that and all other p values are not significant (figure 2). This suggests that most of the *APOE*-related differences in hypometabolism are mediated by PiB.

Regional hypometabolism and regional PiB (figure 3) show strong associations in typical AD-signature regions (angular gyrus, posterior cingulate, precuneus, temporal and parietal regions). The effect is relatively widespread, but non–AD-signature regions such as frontal regions show much less association of hypometabolism with PiB.

Penalized logistic regression identified a parsimonious subset of regions that provide independent information for predicting PiB >1.5 while at the same time protecting against overfitting due to considering a total of 47 regions. We found the key hypometabolic regions to be the angular gyrus and posterior cingulum, with each contributing independent predictive information.

The correlation between AD-signature regions and global PiB was −0.22, significantly higher than the correlation between non–AD-signature regions of FDG and global PiB (−0.06 to −0.14; $p < 0.001$ for all regions). The correlation between AD-signature regions and regional PiB was −0.23, also significantly higher than the correlation between non–AD-signature regions of FDG and regional PiB (−0.02 to −0.12; $p < 0.001$ for all regions) (table e-1 on the *Neurology*® Web site at Neurology.org).

DISCUSSION These data demonstrate regional hypometabolism on FDG-PET is associated with PiB retention in normal subjects. Notably, this hypometabolism becomes evident in low PiB SUVR ranges widely used as a cutoff for distinguishing normal and abnormal PiB (approximately 1.5).[6,11] In the groups with greatest PiB accumulation, greater hypometabolism occurs. This implies that these 2 pathologic biomarker events are linked closely in a dose-related manner. The present observations are consistent with prior reports but also demonstrate hypo-metabolism associated with minimal amyloid burden as well as an incremental dose relationship of the biomarkers in a population-based study that is generalizable to the population at large. In addition, we have shown that the association of hypometabolism and amyloid accumulation also occurs in a regional, individual ROI basis and is more significant in AD-signature regions.

Prior data published on hypometabolism in CN subjects have been inconsistent. For example, hypometabolism has been shown to occur in "at-risk" normal subjects through the spectrum of disease to subjects with AD in AD signature patterns (posterior cingulate, precuneus, parietal and temporal regions).[12–17] Some reports have demonstrated that hypometabolism may be more closely associated with *APOE* status than with amyloid deposition.[18] Others have described increased metabolism associated with increased amyloid accumulation in AD vulnerable regions (e.g., posterior cingulum and precuneus) in normal subjects and in subjects with mild cognitive impairment. They have suggested that hypermetabolism may be the initial metabolic perturbation on the AD neurodegenerative cascade.[19,20] The finding of increased metabolism is difficult to reconcile given other data showing that typical AD patterns of hypometabolism occur in high-risk normal subjects even at young ages and that hypometabolism in normal subjects has been shown to be a predictor of progression to AD in pathologically verified AD cases.[21–23] We were unable to identify any consistent hypermetabolic associations in our population on our ROI analysis. Some of the discrepant findings between these prior studies showing hypermetabolic associations and the present work could possibly be attributable to increased noise introduced by a limited number of subjects. None of the previous work had more than 52 normal subjects included.

This work is limited by the fact that the eventual disease outcome of the normal subjects is unknown. Amyloid-positive normal subjects may die without any dementia or they may develop different neurodegenerative diseases.[24,25] Another weakness of this work is that by defining our "negative" PiB population as those with an SUVR of 1.4, we are limited in our ability to assess hypometabolism that might occur already in this group. In addition, this work is not intended to define or validate a PiB cutoff. Unraveling these issues will require longitudinal study to provide disease outcome and autopsy correlation.

**Figure 1   Global cortical PiB vs regional FDG**
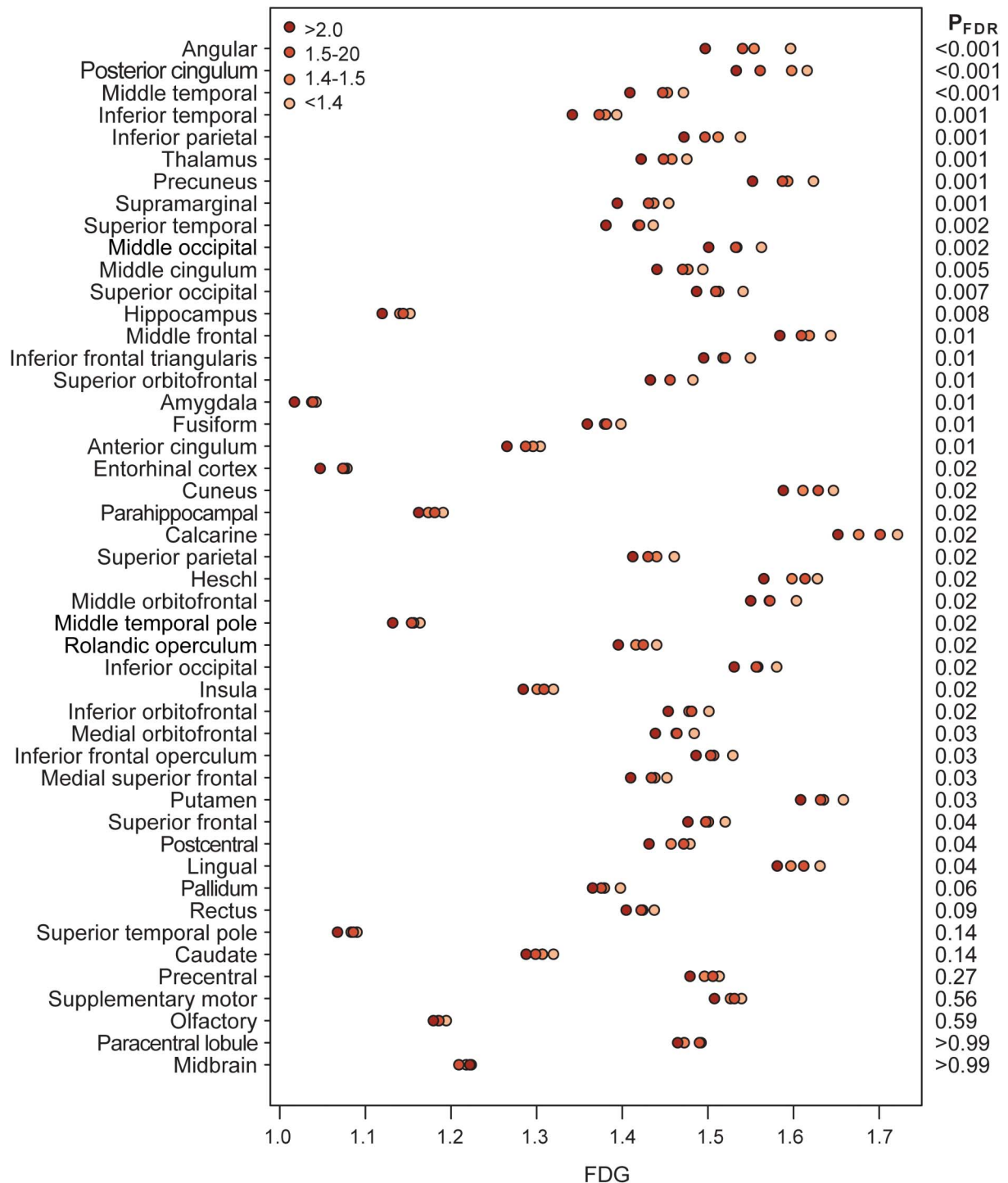
Age- and sex-adjusted mean FDG within each PiB group for the 47 regions of interest. The regions are sorted by level of significance. The estimates assume an 80-year-old subject and represent the average FDG for both men and women. The right side of the plot indicates the FDR-corrected p value for a "dose-effect" test of whether the log of PiB is associated with regional FDG after accounting for age and sex. FDG = [18F]-fluorodeoxyglucose; FDR = false discovery rate; PiB = Pittsburgh compound B.

Prior investigations have demonstrated subtle but detectable hypometabolism in AD-signature regions in CN very young subjects (20–39 years) who are *APOE* ε4 carriers when they may be unlikely to have amyloid accumulation, although amyloid status was not documented in this group.[23] In small samples, others have not been able to identify amyloid-positive scans in similar young subjects in their 30s, supporting the idea that amyloid accumulation may be a later event.[26] In addition, in *APOE* ε4 carriers, amyloid accumulation appears to be related to gene dose with homozygotes demonstrating greater brain

Figure 2 ROI analysis of hypometabolism stratified by *APOE* status
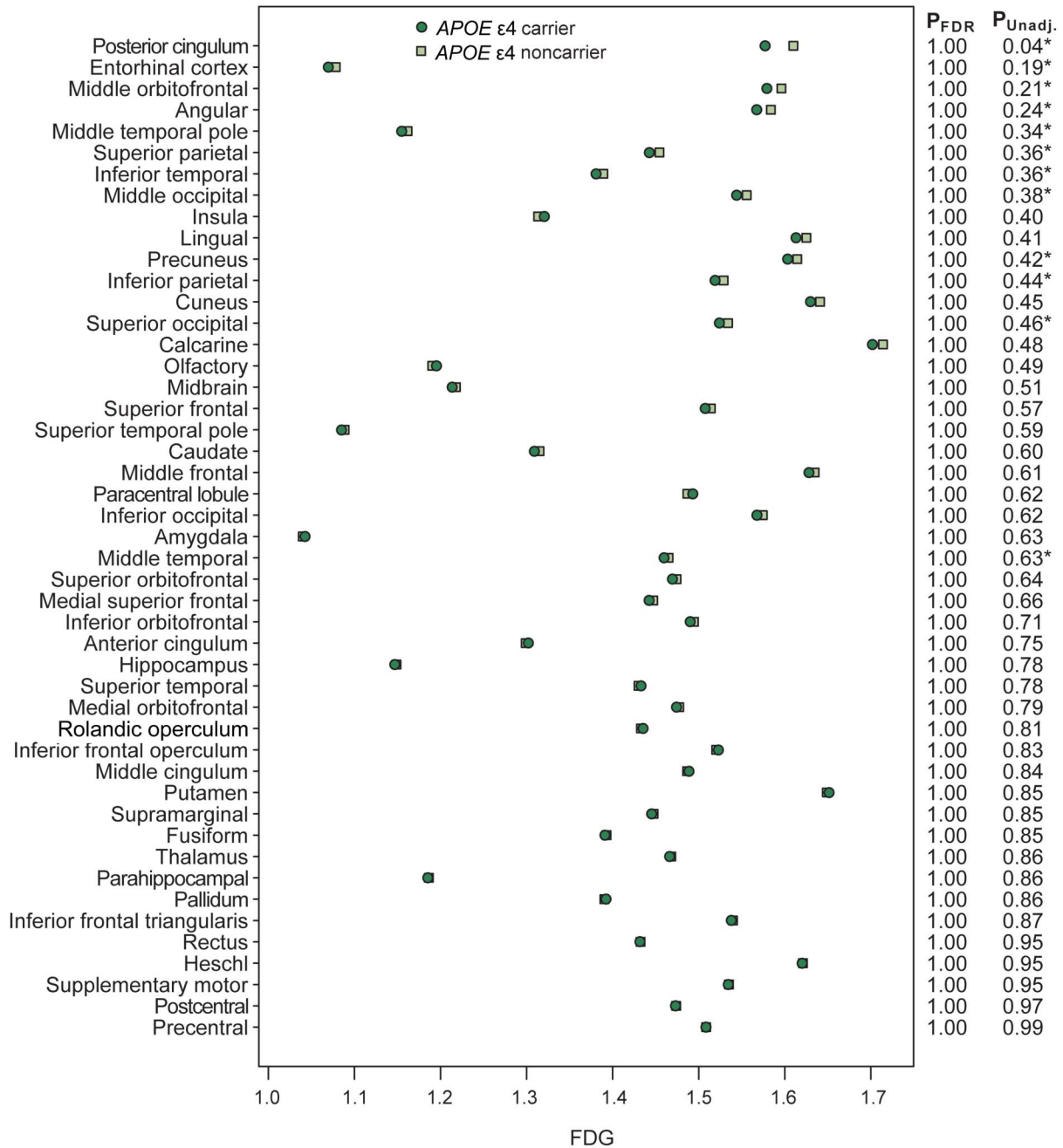
Age- and sex-adjusted mean FDG for *APOE* ε4 carriers and noncarriers by region. The regions are sorted by level of significance based on unadjusted *p* values. The estimates assume an 80-year-old subject with PiB of 1.4 and represent the average FDG for both men and women. The first column of *p* values on the right side of the plot is FDR-corrected *p* values from a test of *APOE* after adjusting for age, sex, and PiB. The second column shows unadjusted *p* values. An asterisk is used to indicate regions in which *APOE* was significant at the $p < 0.10$ level after adjusting for age and sex but not PiB. FDG = [18F]-fluorodeoxyglucose; PiB = Pittsburgh compound B; ROI = region of interest.

amyloid, suggesting that the ε4 allele may be driving amyloid accumulation[27] and may be associated with hypometabolism. Our data cannot confirm the *APOE* ε4 gene dose effect because we had only 10 *APOE* homozygotes in our sample, but increasing frequency of *APOE* ε4 carrier status does occur with increasing PiB dose in our population (table 1). We likewise cannot confirm amyloid PET findings in the young. Nevertheless, these prior observations suggest

that hypometabolism occurs in association with *APOE* ε4 carriage, possibly without, or before, amyloid accumulation. Our data show that the association of hypometabolism and brain amyloidosis is not contingent on *APOE* ε4 status in normal subjects. In fact, in the current study, the subjects with *APOE* ε4 do not have significantly more hypometabolism than those without, suggesting that in this elderly cohort, after accounting for amyloid load, *APOE* ε4 does not

Figure 3 Regional hypometabolism associated with regional PiB

Age- and sex-adjusted mean FDG within each regional PiB tertile. The regions are sorted by level of significance. The estimates assume an 80-year-old subject and represent the average FDG for both men and women. The right side of the plot indicates the FDR-corrected p value for a "dose-effect" test of whether the log of regional PiB is associated with regional FDG after accounting for age and sex. FDG = [18F]-fluorodeoxyglucose; FDR = false discovery rate; PiB = Pittsburgh compound B.

significantly worsen hypometabolism in the AD-signature brain regions in this population.

The previous findings of hypometabolism from young *APOE* ε4 carrier populations and our aging population are not discrepant but complementary and thought-provoking in our view. We have demonstrated that *APOE* ε4 carriers demonstrate hypometabolism closely linked with amyloid accumulation and that hypometabolism is associated with PiB positivity in *APOE* ε4 noncarriers that is similar to that seen in

carriers. Much of the association we see between FDG and *APOE* ε4 is attributable to the relationship between PiB and *APOE* ε4. We interpret these data to likely mean that *APOE* ε4 status alone can induce hypometabolism, and that amyloid deposition alone can induce similar hypometabolism, especially in AD-signature cortical regions. Any potentiation of prior *APOE* ε4–related, nonamyloid-induced hypometabolism with an entirely different mechanism could be possible but we do not have data to make that

distinction. We see that the hypometabolic effect of amyloid clearly occurs independently of *APOE* ε4 positivity in *APOE* ε4–negative normal elderly subjects and speculate whether distinct mechanisms may be at work to induce the hypometabolism seen in young amyloid-negative, *APOE* ε4–positive vs elderly amyloid-positive, *APOE* ε4–positive subjects.

Previous basic science work on the mechanisms of hypometabolism and work in *APOE* ε4 interaction has shown that both amyloid and *APOE* ε4 can independently affect metabolism. In neuronal cell lines, amyloid accumulation alone can cause mitochondrial dysfunction with impaired energy metabolism.[28] In addition, human amylin, amyloid protein deposited in the pancreas in patients with diabetes, also perturbs mitochondrial function.[29] Likewise, *APOE* ε4 fragments alone have been associated with reduced expression of genes encoding for cytochrome oxidase leading to mitochondrial dysfunction with impaired oxidative metabolism as shown histochemically in the posterior cingulate.[30,31] Direct effects of *APOE* on the endoplasmic reticulum could also lead to decreased glucose uptake in cells.[32]

Additional ideas relative to hypometabolism mechanisms associated with amyloid, which could be especially pertinent to our aging subjects, may be that chronic diseases seen frequently in aging and associated with AD can lead to mitochondrial dysfunction through amyloid deposition in target tissues. Examples of this include diabetes[29,33] and hypertension.[34] This could implicate an intermediary step whereby chronic disease–linked amyloid deposition induces metabolic abnormalities. This concept could add merit to a multifactorial cascade argument for AD

in which any one or a combination of these diseases could be causative. Evaluations of each of these individual disease contributions to, and relationships with, early hypometabolism and amyloid deposition are ongoing avenues of investigation in our population.

In recent hypothetical models of AD biomarker pathology that we and others initially proposed describing the temporal evolution of AD biomarkers, the alterations in brain metabolism that occur on the AD cascade had been postulated to occur years after amyloid accumulation had reached a "pathologic" PiB (SUVR of 1.5) threshold.[35,36] The present data support a closer association of hypometabolism and amyloid deposition at lower levels and help to validate our more recent hypothetical model.[2] Our present data suggest that amyloid accumulation and hypometabolism are more likely to occur simultaneously throughout the spectrum of brain amyloid levels. Figure 4 illustrates this relationship by using the PiB threshold of 1.5 as the "positive" level, with coexisting hypometabolism shown as predicted by the data in the present work, and projects the change in PiB and FDG measurements over time based on our prior work determining the rates of change of PiB at 0.07 SUVR per year[37] and FDG-PET (in PiB-positive subjects) at 0.017 SUVR per year[38] in serially studied subjects in our population. We also incorporated the idea that hypometabolism continues to worsen throughout life in patients with AD (even while amyloid levels appear to plateau), as supported by prior work.[39] Other authors have estimated that it takes 9 years for amyloid accumulation to progress from the normal SUVR of 1.2 (the average low PiB-PET value in their normal population) to an SUVR of 1.5 that is

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Figure 4   Theoretical relationship of brain amyloid load and hypometabolism in AD
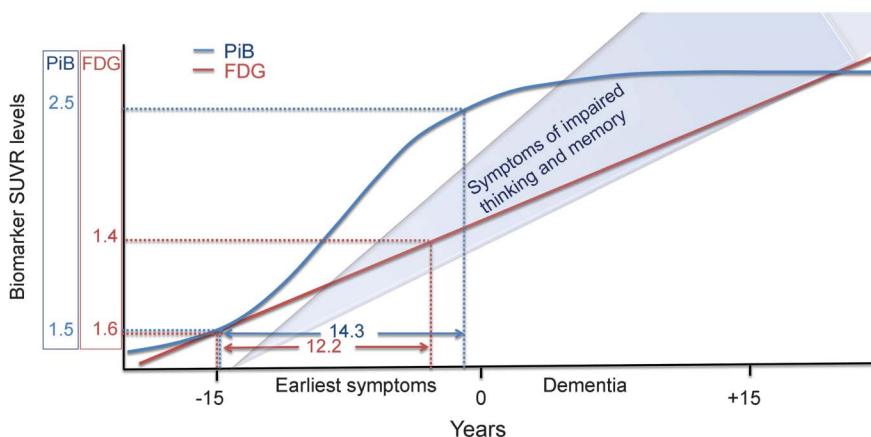
Theoretical dose relationship of brain amyloid load (blue SUVR) and hypometabolism (red SUVR) predicted in normal subjects from these data. The biomarker relationships are estimated for relative to future disease status categorizations as "early symptoms" and "dementia" on the x-axis timeline. The SUVR projections are based on the initial SUVR relationships starting at a PiB SUVR of 1.5 and thereafter projected based on previously determined yearly change rates for PiB and FDG SUVR values in this population. AD = Alzheimer disease; FDG = [18F]-fluorodeoxyglucose; PiB = Pittsburgh compound B; SUVR = standardized uptake value ratio.

considered pathologic.[4] In addition, we must consider that low amyloid (below 1.5) or very low hypometabolism may not be detectable with today's technology. Also, we have no data determining which occurs first at these lowest levels.

This discussion is made more interesting by recent data demonstrating that some level of amyloid plaque burden likely precedes the development of toxic Aβ oligomers that lead to neurotoxicity. A recent report claimed that once a small but critical concentration of amyloid fibrils has accumulated, toxic oligomeric species are predominantly formed from monomeric peptide molecules through a fibril-catalyzed secondary nucleation reaction, rather than through a classic mechanism of homogeneous primary nucleation.[40] This is in contrast to the theory that Aβ oligomers form first and then form fibrils. We can hypothesize from these data and our PET imaging data that a pathologic threshold of amyloid fibril accumulation, sufficient to catalyze formation of toxic oligomeric Aβ, is occurring at a PiB SUVR of at least 1.5. Left open to question is whether minimal levels of amyloid lower than 1.5 exert any neurotoxic effect seen as hypometabolism or otherwise, and requires more longitudinal and serial individual data to resolve.

Intervention trials in the normal elderly may benefit from using these data to target therapy to those with amyloid and hypometabolism and in that way have the greatest potential for treating a "functionalized" AD cascade. The corollary to our observations in the aging population and treatment trials is that treatment of AD may need to be individualized in patients depending on the primary cause of neurodegeneration. Diabetes or hypertension may also need to be managed aggressively and monitored in intervention trials. Consideration of these possibilities may enhance the chances of success of future clinical trials.

AUTHOR CONTRIBUTIONS

Dr. Lowe designed the study, took part in data collection, performed and supervised all analyses, generated the first and final drafts, and takes overall responsibility for the data and the manuscript. Mr. Weigand performed data analyses and critically reviewed the manuscript. Mr. Senjem and Dr. Vemuri performed analyses of imaging data and critically reviewed the manuscript. Mr. Jordan acquired image data, performed analyses, and critically reviewed the manuscript. Dr. Kantarci, Dr. Boeve, Dr. Jack, Dr. Knopman, and Dr. Petersen took part in data collection and critically reviewed the manuscript.

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DISCLOSURE

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