The effect of β-amyloid positivity on cerebral metabolism in cognitively normal seniors

Andrea C. Bozoki a,b,c,*, Monica Zdanukiewicz c, David C. Zhu b,c,d, for the Alzheimer’s Disease Neuroimaging Initiative 1

aDepartment of Neurology, Michigan State University, East Lansing, MI, USA
bDepartment of Radiology, Michigan State University, East Lansing, MI, USA
cNeuroscience Program, Michigan State University, East Lansing, MI, USA
dDepartment of Psychology, Michigan State University, East Lansing, MI, USA

Abstract

Introduction: We evaluated the effect of cerebral amyloid-β (Aβ) deposition in cognitively normal (CN) seniors on regional metabolism of specific brain regions known to be affected by p-tau deposition.

Methods: Fluorodeoxyglucose positron emission tomography (FDG-PET), volumetric magnetic resonance imaging scans, and global amyloid standardized uptake value ratios (SUVr) were obtained for 210 CNs from the Alzheimer’s Disease Neuroimaging Initiative-2 (ADNI2). Region of interest (ROI) extraction was used to obtain functional SUVr from six bilateral ROIs: amygdala (AM), entorhinal cortex (EC), hippocampus, lateral orbitofrontal, posterior cingulate (PC), and middle temporal gyrus. Every metabolic SUVr set was averaged and analyzed against the corresponding subject’s amyloid SUVr. Correlation analyses were conducted on the full group and between APOE ε4-positive and APOE ε4-negative subgroups.

Results: The APOE ε4+ group exhibited significantly higher metabolism in the EC (r = 0.270, P = .038) and AM (r = 0.267, P = .041). When a significance of the difference test was conducted between the APOE ε4+ and APOE ε4-groups, these same regions remained significant: P = .012 and P = .016, respectively. By contrast, the APOE ε4 group displayed only the conventionally expected result of reduced regional metabolism in the PC (r = −0.161, P = .048), with higher Aβ load.

Conclusions: The effect of amyloid positivity on brain metabolism is regionally specific, and APOE ε4 status substantially modulates regional glucose uptake in these regions. The APOE ε4 allele may cause earlier emergence of clinical symptoms in AD via a mechanism that influences regional metabolic demand in specifically those regions where p-tau deposition is known to occur earliest.

© 2016 the Alzheimer’s Association. Published by Elsevier Inc. All rights reserved.

Keywords: ADNI; FDG-PET; Florbetapir-PET; APOE; Amyloid

1. Introduction

The symptoms of Alzheimer’s disease (AD) are known to be preceded by a long period of silent gradual pathological change [1,2]. Accumulation of amyloid β (Aβ) occurs in cognitively intact older people [3,4], preceding development of symptoms by several decades [5]. In addition, in developing AD, fluorodeoxyglucose positron emission tomography (FDG-PET) studies typically demonstrate cerebral hypometabolism early on, beginning in the...
posterior cingulate (PC), with the precuneus, posterior temporal and lateral parietal regions additionally becoming hypometabolic over time [6,7]. This relationship is affected by APOE ε4 status, with cognitively normal (CN) carriers demonstrating a significantly lower uptake of fluorodeoxyglucose (FDG)—albeit small in magnitude—in specific brain regions, including the PC, precuneus, lateral parietal, and an “AD-signature meta-ROI” [8].

It has been widely assumed that preclinical subjects exhibit normal metabolism. However, recent work suggests that high-risk asymptomatic individuals such as those with high Aβ, can present subtle regional declines in metabolism compared with those without [9–11]. More remarkably, one of these studies showed these same individuals as presenting a relatively higher metabolism in a different region, the medial temporal lobe [10], whereas several others found increased metabolism in medial frontal, lateral prefrontal cortices, and the anterior and/or inferior temporal regions [12,13]. The study by Yi et al. also noted that this relative elevation of metabolism was more pronounced in APOE ε4 carriers, regardless of cerebral amyloid load.

Of the regions mentioned as showing greater FDG uptake in persons with high cerebral Aβ levels, the medial temporal lobe is most relevant, as it is the earliest cortical region to develop the other characteristic pathology of AD, neurofibrillary tangles (NFTs) [14,15]. The trajectory of involvement begins in the entorhinal cortex (EC), spreads to adjacent amygdala and/or hippocampus (AM/HIPP) followed by other portions of the limbic system and eventually involves neocortical regions. Haiko and Eva Braak termed involvement of these regions as stages I, II, III/IV, and V/VI, respectively, with stages I, II, and III still compatible with normal cognition. In conjunction with these pathologic data, there is a large body of work supporting the close relationship of elevated cerebrospinal fluid (CSF) tau levels with cognitive decline, abnormal levels of which occur far closer in time to the onset of clinically apparent symptoms than the appearance of cerebral Aβ [16,17]. However, it is still unknown whether CSF tau levels increase substantially at Braak & Braak stages I, II, or only III.

We hypothesized that, early in the course of NFT deposition, clinically healthy individuals with a high burden of cerebral amyloid would demonstrate subtle regional increases in metabolism in those medial temporal regions corresponding to Braak stages I and II (and possibly III), correlating with progressive involvement of these regions by NFT-laden neurons at a stage when, despite cell death, many neurons in these regions were still relatively healthy and could thus keep up with higher metabolic demand. Furthermore, we hypothesized that CSF p-tau levels would correlate with the elevated metabolism in these same regions if we were capturing individuals who were already undergoing neuronal cell death, when levels of extracellular, soluble p-tau are high enough to be detected by assays. Finally, given the younger age of onset and more rapid clinical decline in APOE ε4+ patients, we explored the possibility of a differential relationship between genotypes and the emergence of higher metabolic demands during the preclinical phase of AD development.

2. Methods

2.1. Subjects

Data used in the preparation of this article were obtained from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu; see Supplementary Data 1). Our image data consisted of T1-weighted high-resolution volumetric magnetic resonance and FDG-PET images of healthy controls downloaded from the ADNI database over the course of the study, the latest in August 2014 (http://adni.loni.usc.edu). Additional data used for the study included subject APOE ε4 status, CSF p-tau, and global amyloid standardized uptake value ratios (SUVr). The individual ADNI subject identifiers used in this study can be found in Supplementary Data 2.

2.2. Standard protocol approvals, registrations, and patient consents

The ADNI was approved by the institutional review board at each site and was compliant with the Health Insurance Portability and Accountability Act. Written consent was obtained from all participants.

2.3. Magnetic resonance image acquisition and preprocessing

All participants who were newly enrolled in ADNI were scanned using a high-resolution 3T volumetric magnetic resonance imaging (vMRI) protocol during screening (http://adni.loni.usc.edu/methods/mri-analysis/mri-acquisition). Images downloaded for the study had undergone the maximum level of correction (i.e., warping, intensity correction, and scaling for gradient drift using the phantom data) and were identified with “N3” and “scaled” in the file name. Further information can be found in the ADNI Alzheimer’s Disease Neuroimaging Initiative 3T MRI Technical Procedures Manual.

2.4. Positron emission tomography (PET) image acquisition and preprocessing

The ADNI acquires florbetapir (AV45) and FDG-PET scans from all newly enrolled participants on two separate days. Scans may be performed in any order, but both must be completed within 2 weeks of the in-clinic assessments at baseline. FDG-PET scans downloaded for this study had...
undergone the maximum level of correction (i.e., coregistered dynamic, averaged, standardized image and voxel size, and uniform resolution). Of note, ADNI FDG-PET data are normalized to a global SUVr: an averaged image is generated from the six individual coregistered frames and then intensity normalized using a subject-specific mask so that the average of voxels within the mask is exactly 1. This process, and a subsequent image smoothing step, is done to make comparison of data from different scanners more straightforward. Further details on ADNI PET methods can be found at adni.loni.usc.edu/data-samples/pet/.

AV45-PET scans were not downloaded for direct analysis in the study. These scans were analyzed by the University of Utah. We chose to use a mean amyloid SUVr value derived from temporal and parietal association cortex amyloid made available on the ADNI site (UU–PET Analysis, v.2014-1-31) under the variable name “AVEASSOC.” These AV45 scans were normalized to cerebellum. A complete description of their method for deriving these values can be found in UU–PET Analysis Methods located at adni.loni.usc.edu.

### 2.5. MR and PET image postprocessing and coregistration

Analysis of Functional NeuroImages (AFNI; http://afni.nimh.nih.gov/) was used for all post-processing conducted to coregister vMR images to their respective FDG scans. All images were refit to original space, centered, and aligned to their partnering data set. Volumetric scans that were acquired obliquely were reoriented and resliced to cardinal coordinate space before centering and realignment; similar steps were taken for respective PET images. Visual inspection was used to evaluate individual coregistration to ensure accuracy.

### 2.6. ROI creation and SUVr acquisition

FreeSurfer was used for image segmentation and the creation of anatomical ROIs [18]. After reconstruction and segmentation, we extracted six of these bilaterally parcellated areas for use as ROI masks in the glucose uptake analysis: EC, AM, HIPP, PC, middle temporal gyrus (MTG), and lateral orbitofrontal (LOF) gyrus. AFNI was then used to obtain the SUVr for each ROI from the coregistered FDG-PET. All coregistered ROI masks were visually inspected and corrected where necessary to ensure accurate data extraction.

### 2.7. Genetic and biomarker acquisition


### 2.8. Statistical analysis

Analyses were done with SPSS 22 (SPSS, Inc., Chicago, IL, USA). Independent t-tests were performed for all demographic variables. FDG-SUVr values from the two hemispheres were averaged for each subject before statistical analysis, yielding a single mean value per ROI. The distribution of glucose uptake values in all six examined brain regions was normally distributed; thus, Pearson correlation was performed to examine the relationship between amyloid burden and ROI glucose uptake, as well as the relationship between p-tau and ROI glucose uptake. A significance of difference between two correlations test [19,20] was then used to directly compare APOE ε4+ and APOE ε4-groups for each of the six bilateral ROIs. Significance was based on a two-tailed analysis with $P < .05$. Stepwise regression was conducted to determine if age, gender, or level of education acted as confounding factors in the APOE ε4 group analyses.

### 2.9. Subject disposition and demographic characteristics

A total of 211 CN individuals matched the necessary inclusion criteria. The mean age and education level for the whole group was 74.2 (6.3) and 16.6 (2.5), respectively. There were 104 men in the pool. Age, education, and gender were not significantly different between groups. Of the total, 152 had no APOE ε4 allele, 53 had one, and six had two alleles. APOE ε4 values of 0 were categorized as the negative group, and values of 1 and 2 were combined to form the positive group. Overall, 165 of 211 subjects had CSF p-tau values recorded: 120 of 152 in the APOE ε4-sample and 45 of 59 APOE ε4+ (Table 1).

### 3. Results

#### 3.1. SUVr correlation analysis

Although there were no significant associations between Aβ deposition and FDG-SUVr when the entire CN group was examined together, the APOE ε4+ subgroup exhibited significantly higher rates of metabolism in both the EC ($r = 0.270, P = .038$) and AM ($r = 0.267, P = .041$) with increasing amyloid load, and these two regions remained significant when a significance of the difference test was conducted between the APOE ε4+ and APOE ε4-subjects (EC $Z = 2.506, P = .012$ and AM $Z = 2.407, P = .016$, respectively). APOE ε4-subjects showed a negative correlation between Aβ deposition and FDG-SUVr in the PC:

<table>
<thead>
<tr>
<th>Variable</th>
<th>n = 211</th>
<th>APOE ε4-</th>
<th>APOE ε4+</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y (standard deviation [SD])</td>
<td>74.2 (6.3)</td>
<td>74.6 (6.0)</td>
<td>73.1 (7.0)</td>
<td>.13</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>107 (50.7)</td>
<td>74 (49)</td>
<td>33 (55.9)</td>
<td>.37</td>
</tr>
<tr>
<td>Education, y (SD)</td>
<td>16.6 (2.5)</td>
<td>16.7 (2.5)</td>
<td>16.2 (2.6)</td>
<td>.19</td>
</tr>
</tbody>
</table>
r = −0.161, P = .048, but this difference was no longer significant when the APOE e4+ and e4− groups were directly compared using the significance of the difference test. We did not correct for multiple comparisons because our a priori hypothesis was such that we expected to see differences only in ROIs affected at preclinical Braak & Braak stages and included later-stage ROIs primarily to serve as control regions (Table 2 and Fig. 1).

3.2. P-tau correlation analysis

Consistent with prior reports [21,22], CSF p-tau levels correlated strongly with amyloid burden in this CN group (r = 0.267; P = .001). This relationship was also true for APOE e4 considered separately (r = 0.239; P = .009), although the smaller group size of APOE e4+ who had CSF results did not demonstrate this same relationship (r = 0.281; P = .061; Table 3 and Fig. 2).

As with the FDG–amyloid relationship, there were no significant findings in the total sample between FDG-SUVr and CSF p-tau levels in any of our examined regions. In the APOE e4+ subgroup, however, we did find significant relationships between p-tau and EC (r = 0.307, P = 0.040), p-tau and LOF (r = 0.322; P = .031), and p-tau and MTG (r = 0.378; P = .011). There were no significant findings in any examined ROI for the APOE e4-subgroup. Unlike our examination of the FDG–amyloid relationship, the p-tau regional findings did not survive direct comparison using the significance of differences test.

4. Discussion

Our findings indicate that: (1) the effect of amyloid positivity on brain metabolism is regionally specific: medial temporal regions (EC and AM, although not HIPP), which are the first to develop p-tau pathology, show greater effects than temporal neocortex, orbitofrontal regions or PC gyrus, which only accrue substantive numbers of NFTs during clinically symptomatic disease; and (2) APOE e4 status substantially modulates regional glucose uptake in these regions, such that greater amyloid load is not correlated with regional metabolism in APOE e4-individuals, but a positive correlation with metabolism is seen in these same regions in the APOE e4+ group. Intriguingly, several groups have reported that this same phenomenon is even more robustly present in individuals with Down syndrome (DS) before the development of AD [23,24]. The authors, based on both direct pathologic examination of their DS subjects, whose age range was between 5 months and 67 years, along with examinations of a rodent model of EC tau pathology, hypothesize a compensatory synaptic and neurite outgrowth in response to the evolving p-tau protein pathology. If APOE e4 positivity increases the vigor of this compensatory metabolic response similar to having a third copy of the APP gene (and/or a homologue of the β-site APP cleaving enzyme which is also located on c21), it suggests one mechanism by which the APOE e4 allele may cause earlier emergence of clinical symptoms in AD. It also suggests that, for these individuals, a therapeutic approach that provides for the increased energy needs of these neurons may help protect this vulnerable population and provides an explanation for the differential effects of certain antiamyloid therapies based on APOE status. A better understanding of prodromal metabolic derangements in key brain regions may allow different therapeutic options to be targeted to the patient population and stage of pathology at which they can still affect a change.

Our examination of the relationship between amyloid and p-tau in this CN population was somewhat more complicated. Although we demonstrated a strong positive correlation between global amyloid burden and CSF p-tau concentration (as have many other groups) in the overall group and the APOE e4− subgroup, this relationship did

<table>
<thead>
<tr>
<th>Group</th>
<th>p-tau</th>
<th>EC SUVr</th>
<th>AM SUVr</th>
<th>HIPP SUVr</th>
<th>LOF SUVr</th>
<th>MTG SUVr</th>
<th>PC SUVr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole group (N = 211; p-tau N = 165)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson</td>
<td>.267</td>
<td>.025</td>
<td>.006</td>
<td>−.014</td>
<td>−.109</td>
<td>−.040</td>
<td>−.097</td>
</tr>
<tr>
<td>P value</td>
<td>.001</td>
<td>.722</td>
<td>.929</td>
<td>.835</td>
<td>.114</td>
<td>.566</td>
<td>.160</td>
</tr>
<tr>
<td>APOE e4-negative group (N = 152; p-tau N = 120)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson</td>
<td>.239</td>
<td>−.011</td>
<td>−.013</td>
<td>−.083</td>
<td>−.016</td>
<td>−.098</td>
<td>−.059</td>
</tr>
<tr>
<td>P value</td>
<td>.009</td>
<td>.158</td>
<td>.207</td>
<td>.312</td>
<td>.048</td>
<td>.230</td>
<td>.469</td>
</tr>
<tr>
<td>APOE e4-positive group (N = 59; p-tau N = 45)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson</td>
<td>.281</td>
<td>.270</td>
<td>.267</td>
<td>.168</td>
<td>.096</td>
<td>.155</td>
<td>−.200</td>
</tr>
<tr>
<td>P value</td>
<td>.061</td>
<td>.038</td>
<td>.041</td>
<td>.204</td>
<td>.471</td>
<td>.240</td>
<td>.128</td>
</tr>
<tr>
<td>Significance of the difference between APOE e4 groups</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Z-score</td>
<td>−.250</td>
<td>−.256</td>
<td>−.247</td>
<td>−.169</td>
<td>−.165</td>
<td>−.162</td>
<td>.091</td>
</tr>
<tr>
<td>P value</td>
<td>.802</td>
<td>.012</td>
<td>.016</td>
<td>.108</td>
<td>.099</td>
<td>.104</td>
<td>.360</td>
</tr>
</tbody>
</table>

Abbreviations: AM, amygdala; EC, entorhinal cortex; FDG-PET, fluorodeoxyglucose positron emission tomography; HIPP, hippocampus; LOF, lateral orbitofrontal; MTG, medial temporal gyrus; PC, posterior cingulate; SUVr, standardized uptake value ratios.

NOTE. Differences with P values <.05 are indicated in italic.
not extend to the APOE ε4+ group, likely due to inadequate power. In addition, we found a relationship between p-tau and regional FDG-PET metabolism in the APOE ε4+ group but failed to replicate the regional specificity of this relationship in the predicted manner. That is, there was a correlation of CSF p-tau level with metabolism in EC, but not with AM or HIPP, and there was a relationship with metabolism in LOF and neocortical regions, which are typically less involved with NFT at preclinical stages of AD. The smaller sample size for CSF data combined with the challenge of quantitative p-tau analysis by assay [25] may have contributed to these results.

We set out to systematically examine a set of brain regions that capture the presumed trajectory of tau-tangle spread within the cortex, which begins first in the transentorhinal region of the EC and gradually spreads to encompass, first, AM and HIPP, then adjacent areas of neotemporal and orbitofrontal cortex, and finally, more distant neocortical regions including the PC [14,15,26]. This evolution of NFT pathology occurs in parallel with a similar progression of Aβ deposition, although the latter begins in a spatially widespread way, with simultaneous appearance of plaques in most neocortical association regions during a stage now termed Thal phase I [15,27]. This last is actually a very important point when examining regional brain metabolism: any differences seen on FDG-PET in the EC, AM, and HIPP in amyloid + CN are not due to direct consequences of amyloid toxicity during Thal phase I.

Most intriguingly, our main finding, of increasing metabolism with increasing amyloid load in early NFT-associated brain regions, occurred only in the APOE ε4+ subgroup. This is consistent with the findings of several other recent studies examining the effects of amyloid deposition on brain metabolism. A study by Scheef et al. [10] found increased metabolism in right parahippocampal gyrus and HIPP in subjective memory impaired group compared with controls (regardless of APOE ε4 status, which was ~ 1/3 of their sample). More recently, Oh et al. [12] examined 52 healthy seniors using PiB-PET, FDG-PET, and structural magnetic resonance imaging. Their findings suggested that CN older adults with greater amyloid deposition are relatively hypermetabolic in frontal and parietal brain

Fig. 1. Global amyloid concentration versus regional glucose metabolism for all six ROIs. Scatterplots for each of the six ROIs, with global (association cortices) amyloid SUVr for each subject on the X axis and ROI-specific glucose SUVr on the Y axis. The regression line is drawn separately for APOE ε4-positive and ApoE ε4-negative groups for ease of comparison. Abbreviations: ROI, region of interest; SUVr, standard uptake value ratio.
regions while undergoing gray matter volume loss in overlapping brain regions. Finally, Yi et al. \cite{13} found that APOE ε4 CN had hypermetabolism relative to their APOE ε4-counterparts, although in medial frontal and anterior temporal regions.

Taken together, these results suggest that this genotype modulates the appearance of clinical symptoms by causing a more aggressive, metabolically vigorous response in NFT-evolving regions. Hypermetabolism on FDG-PET can be seen due to mechanisms that increase energy needs of any brain cellular component, including astrocytes, oligodendrocytes, or even indicating the presence of substantial neuroinflammatory cells (activated microglia); thus, it is unclear whether the observed phenomenon has a neuronal

<table>
<thead>
<tr>
<th>Group</th>
<th>EC SUVr</th>
<th>AM SUVr</th>
<th>HIPP SUVr</th>
<th>LOF SUVr</th>
<th>MTG SUVr</th>
<th>PC SUVr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole group (N = 165)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson</td>
<td>0.080</td>
<td>0.144</td>
<td>0.007</td>
<td>0.079</td>
<td>0.134</td>
<td>−0.038</td>
</tr>
<tr>
<td>P value</td>
<td>.306</td>
<td>.065</td>
<td>.933</td>
<td>.311</td>
<td>.087</td>
<td>.626</td>
</tr>
<tr>
<td>APOE ε4-negative group (N = 120)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson</td>
<td>−0.002</td>
<td>0.104</td>
<td>−0.036</td>
<td>0.015</td>
<td>0.058</td>
<td>−0.043</td>
</tr>
<tr>
<td>P value</td>
<td>.987</td>
<td>.257</td>
<td>.698</td>
<td>.868</td>
<td>.532</td>
<td>.643</td>
</tr>
<tr>
<td>APOE ε4-positive group (N = 45)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pearson</td>
<td>0.307</td>
<td>0.253</td>
<td>0.165</td>
<td>0.322</td>
<td>0.378</td>
<td>−0.044</td>
</tr>
<tr>
<td>P value</td>
<td>.040</td>
<td>.094</td>
<td>.279</td>
<td>.031</td>
<td>.011</td>
<td>.775</td>
</tr>
</tbody>
</table>

Significance of the difference between APOE ε4 groups

<table>
<thead>
<tr>
<th>Z-Score</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>−1.775</td>
<td>.076</td>
</tr>
<tr>
<td>−0.857</td>
<td>.391</td>
</tr>
<tr>
<td>−1.126</td>
<td>.260</td>
</tr>
<tr>
<td>−1.773</td>
<td>.076</td>
</tr>
<tr>
<td>−1.889</td>
<td>.059</td>
</tr>
<tr>
<td>0.006</td>
<td>.996</td>
</tr>
</tbody>
</table>

Abbreviations: AM, amygdala; EC, entorhinal cortex; FDG-PET, fluorodeoxyglucose positron emission tomography; HIPP, hippocampus; LOF, lateral orbitofrontal; MTG, medial temporal gyrus; PC, posterior cingulate; SUVr, standardized uptake value ratios.

NOTE. Differences with P values <.05 indicated in italic.

Fig. 2. CSF phospho-tau concentration versus regional glucose metabolism for all six ROIs. Scatterplots for each of the six ROIs, with CSF phosphor-tau concentration for each subject on the X axis and ROI-specific glucose SUVr on the Y axis. The regression line is drawn separately for APOE ε4-positive and APOE ε4-negative groups for ease of comparison. Abbreviations: ROI, region of interest; SUVr, standard uptake value ratio.
origin, although most of the known adverse effects of APOE4 protein affect neurons (by both AB-specific [28,29] and non–AB-dependent mechanisms [30–33]), with some evidence pointing toward direct toxicity of APOE e4 fragments on NFT formation [34,35]. Thus, our findings point toward a compensatory response in regions of NFT formation, either due to increased synapse development and connectivity, or to a stage of sustained or recurrent neuronal excitation (“hyperexcitability”) occurring during NFT production. Either of these events may occur more vigorously in APOE e4+ individuals who experience an earlier and more rapidly progressive form of AD.

It must be acknowledged that not all groups who have examined the relationship between Aβ and FDG metabolism in CN have found hypermetabolic brain regions, although substantial methodologic differences may account for their lack in this area. For example, a 2012 study found no significant relationship at all between amyloid deposition and FDG metabolism. Their use of a single “metaROI” (the mean FDG uptake in a set of ROIs including R/L inferior temporal, lateral parietal, and PCC, relative to pons/cerebellum) in a group of 126 CNs taken from ADNI [36]. It is therefore unsurprising that they found no individual regional effects, as any foci of elevated metabolism would have been lost when averaged with multiple larger brain regions in which eumetabolism or hypometabolism was observed. Another article published that same year [37] noted that an “AD signature” of FDG-PET regional hypometabolism might not actually be strongly tied to amyloid deposition, in describing a group of neurodegeneration+ (by either FDG-PET or vMRI), amyloid—individuals they termed “SNAP.” This study also used a composite ROI approach (comprised of the angular gyrus, PC, and inferior temporal cortical ROIs normalized to pons and cerebellar vermis), which precludes analysis of specific target brain regions. Finally, a recent study of the large Mayo Clinic Aging cohort (600 CN elders) found no hypermetabolism in any examined brain region and no relationship between APOE status and brain metabolism in a group of 600 CN subjects [11]. However, they did not perform the analysis done in this article; that is, they did not compare the range of amyloid positivity between APOE e4+ and APOE e4− groups, they examined only the mean FDG value present at a fixed PiB SUVr of 1.4. Thus, they missed finding the possible relationship between change in regional metabolism and change in PiB SUVr.

In light of the above, we note that there are undoubtedly multiple different causes of hypometabolism, which is a nonspecific sign of neuronal injury. It can be seen due to late-stage/severe amyloid deposition local to those brain regions [36,38]; it may also be seen on a “disconnection” basis in earlier disease states, where it may also be at sites removed from the heaviest burden of amyloid deposition (possibly in neuronal projection areas) [39–41]. This multiple-cause problem may be at the root of why different research groups see the hypometabolism in different brain regions.

Although the causes of hypometabolism are multiple, hypermetabolism strongly implies an increase in local cellular energy needs. Hyperphosphorylation requires adenosine triphosphate (ATP) and vigorous hyperphosphorylation would induce a relative hypermetabolic state in these cells while they were still relatively healthy and could “keep up” with the higher metabolic demand.

The aforementioned hypothesis explains why many other authors have failed to find elevated metabolism in FDG-PET studies of high-risk normal individuals; they are looking in the wrong place. By choosing to examine either brain regions with early and/or heavy amyloid load, or by averaging the metabolism across large portions of the brain, they have missed the relatively subtle signal present in the limited brain regions affected by hyperphosphorylation in preclinical AD. And in fact, this signal is only present in APOE e4+ individuals, (possibly because of the higher rate of pathologic p-tau formation), so, it would also be missed by studies that fail to examine that subgroup specifically. This observation begs the question of whether APOE e4− but high-risk groups (e.g., those with a mutation in the APP gene) would demonstrate this same early relative hypermetabolism in p-tau–susceptible regions.

4.1. Limitations

It is currently unclear whether tau tangles appear in substantial numbers beyond the EC during Thal phase 2 (amyloid in the EC and HIPP CA1 regions), or if phase 3 (amyloid in other parts of the HIPP, plus the deep gray nuclei) is required for this event. It is also unclear what Thal phase is the earliest to come up as “amyloid positive” on a florbetapir scan. These uncertainties regarding the relative ordering of pathologic stages between tau and B-amyloid trajectories argue for additional analyses on large brain bank populations and would help substantially in understanding the relationship (and possible causal linkages) between the two types of pathologic protein accumulation. In addition, as a cross-sectional retrospective study, our analysis captures only a “snapshot in time.” It does not address the evolution of relatively increasing or decreasing metabolism of brain regions in response to progressive amyloid accumulation (and, presumably, to accumulating NFT-mediated neuronal injury). As discussed, timing may be critical in the manifestation of hypermetabolism and hypometabolism, with a preponderance of different ongoing brain insults leading to a different FDG-PET “phenotype” during the long prodromal AD phase at any given time. It will take further data collection and development of more robust methods for getting around test–retest variability in PET imaging before a nuanced understanding
of the trajectory of metabolic change can be examined accurately and merged with the aforementioned neuropathologic correlation to identify which mechanisms of brain damage lead to hypermetabolism and hypometabolism, respectively.

Acknowledgments

The authors thank Dr. Paul Beach, for assistance with data analysis; Michigan State University’s High Performance Computer Center for providing storage space and computing resources. Data collection and sharing for this project was funded by the Alzheimer’s Disease Neuroimaging Initiative (ADNI; National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: Alzheimer’s Association; Alzheimer’s Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen Idec Inc.; Bristol-Myers Squibb Company; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Medpace, Inc.; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Synarc Inc.; and Takeda Pharmaceutical Company. The Canadian Institutes of Rev December 5, 2013 Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer’s Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuroimaging at the University of Southern California.

Authors’ contributions: A.C.B. contributed to conceptual framework, data analysis, and article writing. M.Z. contributed to MR and PET data processing, statistical analysis, and article writing. D.Z. contributed to MR and PET data processing, article review, and editing. Study funding: No targeted funding was reported.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jalz.2016.06.003.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed existing studies of neuronal metabolism as examined by fluorodeoxyglucose positron emission tomography (FDG-PET), in cognitively normal seniors at risk for developing AD and nondemented Down’s patients. Reports of elevated regional metabolism were contrasted with those reporting unchanged or hypometabolism to formulate a hypothesis that elevated metabolism could be related to neuronal regions affected by increased tau phosphorylation.

2. Interpretation: We found regional elevations of FDG-PET metabolism in the specific regions known to harbor the early emergence of tau-mediated damage in individuals with prodromal AD. This metabolic activity was specific to APOE ε4+ individuals.

3. Future directions: Our results need to be validated in a longitudinal study of metabolic change over time. The eventual development of clinical AD in only those individuals showing sequential rising, then falling metabolism in tau-affected regions after Braak stages, would provide a means of identifying preclinical AD with greater certainty in amyloid-positive individuals.

References

1258

A.C. Bozoki et al. / Alzheimer's & Dementia 12 (2016) 1250-1258


