ScienceDirect

IFAC PapersOnline CONFERENCE PAPER ARCHIVE

IFAC PapersOnLine 51-27 (2018) 396–401

Modeling Spatial and Temporal Patterns of APOE ε4 Mediated Glucose Uptake in Mild Cognitive Impairment and Normal Controls

Xueqi Chen*,,#. Manish Paranjpe**,#**
Rongfu Wang*. David Dagan Feng*. Yun Zhou**,&**
for the Alzheimer's Disease Neuroimaging Initiative **

**Department of Nuclear Medicine, Peking University First Hospital, Beijing, China (e-mail: chenxueqi1989@163.com, rongfu_wang@163.com).*
***The Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, MD 21287 USA (e-mail:mparanj1@jhu.edu, yunzhou@jhmi.edu)*
****BMIT Research Group, School of Information Technologies, University of Sydney, Sydney, Australia (e-mail: dagan.feng@sydney.edu.au)*
*****Group Information: Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: ttp://adni.loni.usc.edu/wpcontent/uploads/how_to_apply/-ADNI_Acknowledgement_List.pdf}*

[#] *These authors contributed equally to the study*

[&] *To whom correspondence should be addressed*

Abstract: Apolipoprotein E (APOE) ε4 allele is a risk factor for developing Alzheimer's disease. In this study, we analyzed longitudinal changes in fluorodeoxyglucose (FDG) uptake between APOE ε4 carriers and non-carriers in normal control (NC) and Mild Cognitive Impairment (MCI) subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI). We reported forebrain and limbic regions that exhibit APOE ε4-mediated declines in FDG uptake over a 96 month period in subjects with MCI but not NCs. Using voxel-based and ROI-based analysis, we compared the longitudinal changes in glucose uptake between APOE ε4 carriers and non-carriers from 34 NCs with no cognitive impairment and 48 subjects with MCI. Parietal, temporal and frontal regions had greater longitudinal decreases in FDG uptake in APOE ε4 carriers compared to non-carriers. The Superior parietal lobe, inferior temporal gyrus, thalamus, caudate, parahippocampal gyrus, fusiform gyrus and middle temporal gyrus showed greater longitudinal decreases in FDG uptake in APOE ε4 carriers compared to non-carriers in subjects with MCI but not NC. These findings suggest APOE ε4 genotype is associated with decline in glucose uptake over time and that specific limbic and forebrain structures exhibit APOE ε4-mediated FDG decline in MCI but not NCs. Our work in identifying the brain regions most associated with APOE ε4 related AD pathophysiology will improve quantitative FDG imaging as a biomarker in precision medicine.

Keywords: Functional neuroimaging, FDG, Alzheimer's Disease, APOE ε4

1. INTRODUCTION

Alzheimer's disease (AD) is characterized by memory loss and cognitive decline (Small et al. 2000). Neurological signatures of AD include amyloid peptide plaques, neurofibrillary tangles, and synaptic dysfunction (Mosconi et al. 2010; Thambisetty et al. 2010). Neuroimaging studies have found glucose hypometabolism and bilateral temporoparietal hypoperfusion in subjects who later develop AD (Mosconi, Perani, et al. 2004).

Previous studies have shown the dose dependent role of apolipoprotein E (APOE) ε4 allele as a risk factor for developing AD, increasing its risk by 2.6 to 14.9 fold and lowering the onset by 7 to 15 years (Farrer et al. 1997; Thambisetty et al. 2010). APOE functions in the central nervous system by delivering cholesterol to neurons (Liu et al. 2013). Despite studies relating the ε4 allele to an increased risk for developing AD, the molecular etiology underlying APOE ε4-mediated risk remains elusive.

An obstacle in AD research is the lack of biomarkers which can be used for the pre-clinical diagnosis and to establish an unbiased outcome measure for clinical trials (Jack et al. 2013; Lo et al. 2011; Rosén et al. 2013). Neurological changes start decades before the first visible symptoms of AD. A recent research has suggested using readouts of the core pathology of AD, including cerebrospinal fluid levels of tau, phosphorylated-tau and β-amyloid (Aβ42), to monitor disease progression (Rosén et al. 2013). Work by Chen et al. has

10.1016/j.ifacol.2019.02.002

revealed that glucose hypometabolism measured through ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET), in combination with other biomarkers, may predict conversion to AD. FDG imaging may therefore be a non-invasive biomarker for AD (Chen et al. 2011, 2016; Mosconi, Perani, et al. 2004).

Functional neuroimaging allows for the characterization of APOE-ε4-mediated phenotypic changes in AD, including its association with glucose hypometabolism (Rosén et al. 2013). Cross sectional studies have used FDG imaging to establish the dose-dependent effect of APOE ε4 on hypometabolism in non-demented adults (Reiman et al. 1996). Longitudinal studies used oxygen-15 PET to compare changes in cerebral blood flow (rCBF) in non-demented APOE ε4 carriers and non-carriers and found greater longitudinal decline in rCBF in APOE ε4 carriers compared to non-carriers in the temporal, parietal, and frontal cortices (Thambisetty et al. 2010).

Existing researches have helped to show APOE-ε4-dose dependent associations between rCBF decline and hypometabolism. However, a lack of longitudinal FDG studies, which are critical to establish the role of APOE in increasing the risk of disease over time, still exists. The aim of this study is to find out if there are any differences in APOE ε4 mediated declines in glucose uptake between subjects with mild cognitive impairment (MCI) and normal controls (NCs). We investigated regional associations between the APOE genotype and longitudinal changes in glucose uptake measured using FDG at voxel-based and region of interest (ROI) based levels over a 96-month follow-up period in 34 age-matched NCs and 48 MCI subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI). This study would allow us to determine the brain regions most sensitive to APOE related changes in FDG uptake.

2. METHODS

2.1 Subjects

We used FDG-PET and neuropsychological data from 34 NCs with no cognitive impairment and 48 MCI subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) ranging from 55 to 85 years of age. Subjects were followed for up to 96 months (mean = 76.7 months; median = 84 months). All data were downloaded from the ADNI clinical data repository (http://www.loni.usc.edu/ADNI/). A detailed explanation of study enrollment criteria and protocols can be found at www.adni-info.org. Subjects underwent PET scanning and structural magnetic resonance imaging (1.5T or 3T) every 6 months for a total follow-up period of either 60, 72, 84 or 96 months depending on the availability of neuroimaging data. The FDG PET scans and magnetization-prepared rapid acquisition gradient echo (MP-RAGE) scans were collected. Participants were tracked to detect changes in neuropsychological testing over the follow-up period.

2.2 APOE genotyping

APOE ε4 genotype information was also downloaded from ADNI database. Individuals homozygous and heterozygous for the APOE ε4 were grouped as APOE carriers (n=32). All other participants were classified as non-carriers (n=50).

2.3 Neuropsychological testing

The Neuropsychiatric Inventory (NPI) questionnaire, Global Clinical Dementia Rating (CDR), Mini-Mental State Examination (MMSE), Functional Assessment Questionnaire (FAQ), Alzheimer's Disease Assessment Scale (ADAS) were administered during each scanning visit to assess cognitive decline associated with dementia.

2.4 PET image acquisition and processing

PET and MRI images were downloaded from http://adni.loni.usc.edu/ and processed using Statistical Parametric Mapping software (SPM8, Wellcome Department of Imaging Neuroscience, London, United Kingdom) and MATLAB (The MathWorks Inc.). The downloaded PET and MRI images were processed using Statistical Parametric Mapping software (SPM8, Wellcome Department of Imaging Neuroscience, London, United Kingdom) and MATLAB (The MathWorks Inc.). All preprocessed mean PET images were coregistered to structural MRI images at each follow-up. The MRI images were normalized to standard Montreal Neurologic Institute (MNI) space using SPM8 with a MRI template provided by VBM8 toolbox, and the transformation parameters determined by MRI spatial normalization were then applied to the coregistered PET images for PET spatial normalization. A total of 34 regions of interest (ROIs) were manually drawn on the MRI template using PMOD software (PMOD Technologies Ltd., Zürich, Switzerland) in standard MNI space. A global cortex was defined as a union of orbital frontal, prefrontal, superior frontal, lateral temporal, parietal, posterior precuneus, occipital, anterior cingulate, and posterior cingulate. The ROI of cerebellum gray matter was used as a reference tissue, and the 34 ROIs including cerebellum were used as template ROIs for all subjects in the standard MNI space. Standard uptake value ratio (SUVR) images relative to the cerebellum ROI for FDG were calculated in the MNI space (image volume: 121x145x121, voxel size: 1.5x1.5x15 mm in x, y, z). Thirty-four ROIs defined in MNI space were applied to the SUVR images for ROI-based SUVR analysis (Chen et al. 2016).

In brief, separate PET frames were aligned to one another, averaged, reoriented and then interpolated into a standard image and voxel size (image volume 160×160×96, 1.5×1.5×1.5 mm in x, y, z). Lastly, all the PET images were smoothed to a uniform resolution of 8 mm in full width at half maximum (FWHM).

2.5 Modeling the longitudinal changes in FDG uptake

Voxelwise PET statistical analysis of the longitudinal changes in FDG uptake between APOE ε4 carriers and non-carriers in MCI and NC group was performed using SPM8

(significance level of 0.005 with cluster volume correction). The clusters were assessed using the Talairach atlas brain (www.talairach.org). R (R version: 3.1.1, www.r-project.org) was used to evaluate the ROI-based longitudinal changes in glucose uptake between different APOE groups. In consideration of some of subjects having different follow-up times and follow-up intervals, only two follow-up scans, baseline/24-month follow-up versus the last scan, were used for the voxel-wise and ROI-based analyses. This protocol was adapted from work by Scarmeas et al (Scarmeas et al. 2004). To compare longitudinal changes in FDG SUVR in the APOE ε4 carriers and non-carriers in MCI and NC individuals, a general linear model was used to adjust for sex and age at baseline or 24-month follow-up in both voxel-wise and ROI-based analysis.

3. RESULTS

3.1 Participant characteristics and longitudinal changes in neuropsychological performance

Statistical analysis showed no significant differences between the APOE ε4 carriers and non-carriers in age, sex distribution, and education level at baseline (p: 0.12-0.90). No statistically significant differences were detected between carriers and non-carriers at baseline in any neuropsychological tests (p: 0.18-0.99). No significant differences in follow-up times between APOE ε4 carriers and non-carriers were observed in either the NC (p=0.29 for baseline versus last and p=0.21 for 24 month versus last) and MCI (p=0.90 for baseline versus last and p=0.70 for 24 month vs. last) groups.

A linear mixed effects model was used to adjust the performance on the neuropsychological tests for baseline age and sex. Longitudinal changes in performance between APOE ε4 carriers and non-carriers in both MCI and NC groups was also compared (data not shown) from both baseline to last and 24 months to last. None of the neuropsychological tests produced significant (p>0.05) differences in the longitudinal changes between APOE ε4 carriers and non-carriers over the study period.

We also compared the diagnosis status (AD, MCI or NC) of the study participants at 24 months follow-up and last follow-up to see if there were differences in the proportion of APOE carriers and non-carriers that converted to AD or AD and MCI in the NC individuals. P values of the difference in the rates of conversion to AD (AD or MCI for the NC group) between APOE ε4 carriers and APOE ε4 non-carriers were 0.15 (two-tailed exact Fisher's test) and 0.30 (two-tailed chi-square test) for the NC and MCI group, respectively.

We then potted a Kaplan-Meier survival curve showing the conversion over time in the MCI and NC groups in Figure 1. Survival plots representing the percent of cognitively normal (for the NC groups) or percent of individuals with MCI (for the MCI group) were generated using a Kaplan Meier estimate. The survival plots represent the probability of not converting to AD for the MCI group and AD or MCI for the NC group.

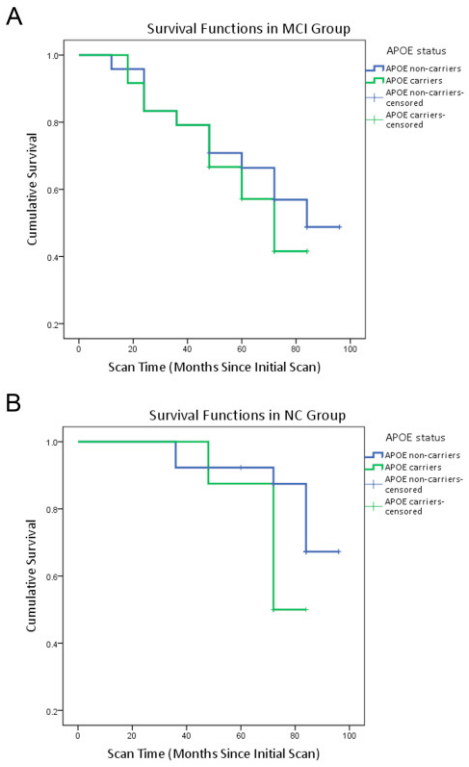

Fig. 1. Survival plots of AD Progression in MCI (A) and NC (B) groups respectively.

In the MCI group, the survival curve shows a cumulative survival of 45% for APOE carriers and 54% for non-carriers. In the NC group, the survival curve shows a survival of 50% for the APOE carriers and 76% for the non-carriers. Both these analyses indicate a non-significant trend towards the APOE carriers having a decreased chance of survival over time, or an increased progression to AD within the follow-up period. Note that the survival curves in Figure 1 are quite stable from baseline to the 24-month follow-up. In light of existing research (Jack et al. 2013) showed that responding years before cognitive symptoms associated with AD for biomarkers such as FDG. We hypothesized the participants in our study may have been observed at earlier stages in which changes in diagnosis status from NC to MCI to AD.

3.2 Voxelwise longitudinal changes in FDG

The APOE carrier vs non-carrier longitudinal changes from baseline scan to the last visit were first evaluated. In the NC group, no supra-threshold clusters were detected by SPM. In the MCI group regions which demonstrated greater longitudinal FDG changes in the APOE ε4 carriers vs non-carriers included: the inferior parietal (cluster of 1102 voxels, peak T = 4.60 at -47 mm, -48 mm, 54 mm in x, y, z), superior parietal (cluster of 1706 voxels, peak T = 3.61 at 39 mm, -64 mm, 51 mm in x, y, z), thalamus and precuneus regions (Fig. 2, upper row).

We then compared FDG uptake from baseline to 24 months follow-up and found that only one cluster, involving the pyramids (peak T = 4.14 at -14 mm, -85 mm, -35 mm in x, y, z, p<0.001) and tuber (peak T = 3.74 at -18 mm, -90 mm, -29

mm in x, y, z, p<0.001) of the cerebellum in NC group showed differential glucose uptake in the APOE ε4 carriers vs non-carriers in the NC group. No significant clusters were detected in the MCI group. Note that both the pyramids and the tuber were not included in our template cerebellum ROI.

Lastly, we used FDG scans from 24 months to the last follow-up for further investigation. In both the MCI and NC groups, we found that clusters in the parietal, temporal, and frontal brain regions had greater longitudinal decreases in FDG uptake in the APOE ε4 carriers as compared to non-carriers (Fig. 2, lower row). Clusters involving the superior parietal lobe, inferior temporal gyrus, thalamus, caudate, parahippocampal gyrus, fusiform gyrus and middle temporal gyrus were found to exhibit APOE ε4-related longitudinal decreases (that is, the APOE ε4 carriers exhibited greater decreases than the APOE ε4 non-carriers in these regions) in the MCI group but not in the NC group. The mean SUVR images created using SPM in standard MNI space in Fig. 3 demonstrate that certain limbic and forebrain regions showed APOE related longitudinal declines in FDG uptake in the MCI group but not NC group.

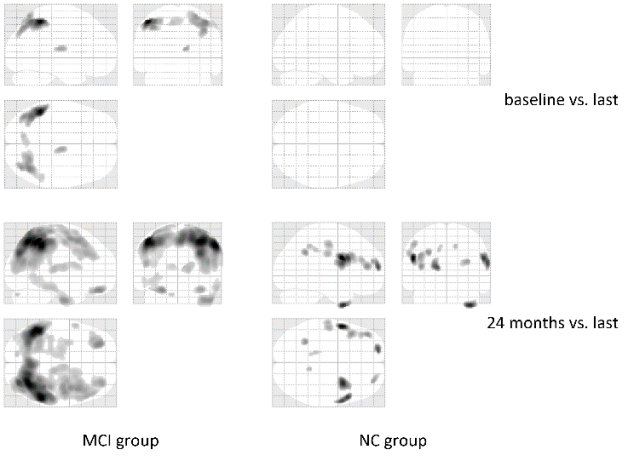

Fig. 2. Differences in Longitudinal Changes in FDG Uptake Between APOE ε4 Carriers and Non-carriers.

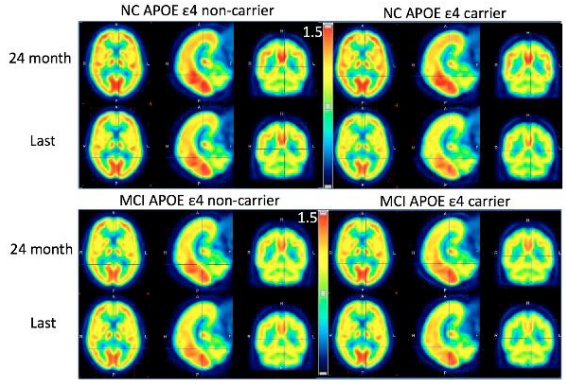

Fig. 3. FDG Mean SUVR Image of APOE Carriers and Non-carriers in MCI and NC group.

3.3 ROI-based longitudinal changes in FDG

ROI SUVRs data was used to perform a ROI-based longitudinal glucose uptake changes analysis between APOE ε4 carriers and non-carriers using a linear mixed model fit by REML (restricted or residual maximum likelihood) criterion. Sex and baseline age were also included as covariates.

ROI parietal and caudate were the only two regions that showed an APOE ε4-related glucose hypometabolism in the MCI group from baseline to the last scan. No regions showed significant APOE ε4-related FDG SUVR declines from baseline to the last follow-up in the NC group. Consistent with the voxelwise analysis, more regions that showed greater decrease in FDG uptake in the APOE ε4 carriers were detected by using the 24-month scan to the last scan (Table 1). The parietal and caudate ROIS were detected only in MCI group, the frontal cortex was detected only in NC group, and the lateral temporal ROI was detected in both groups.

4. DISCUSSION

This study analyzed longitudinal changes in FDG uptake between APOE ε4 carriers and non-carriers in NCs and adults with MCI. Consistent with existing studies, we found parietal, temporal and frontal brain regions had greater longitudinal decreases in FDG uptake in the APOE ε4 carriers compared to non-carriers (Small et al. 2000). Interestingly, we found that the superior parietal lobe, inferior temporal gyrus, thalamus, caudate, parahippocampal gyrus, fusiform gyrus and middle temporal gyrus showed greater longitudinal decreases in FDG uptake in APOE ε4 carriers compared to non-carriers in subjects with MCI but not in normal controls.

Previous studies have linked the APOE ε4 genotype to age-related decreases in cerebral glucose metabolism and blood flow. For example, Thambisetty et al. found, consistent with our results, greater longitudinal decline in rCBF in non-demented APOE ε4 carriers compared to non-carriers in the temporal, parietal, and frontal cortices (Thambisetty et al. 2010). Drzezga et al. compared FDG uptake in APOE ε4 carriers and non-carriers with AD and found a pattern of cerebral hypometabolism in the parietal, temporal, and cingulate cortical areas in carriers compared to non-carriers (Drzezga et al. 2005). A previous water PET found that APOE ε4 carriers exhibited a lower activation in the left lingual gyrus and higher activation in the left cuneus, precuneas, parahippocampal gyrus, and right precentral gyrus (Thambisetty et al. 2010). These results show APOE ε4-related metabolic changes in the forebrain and limbic regions of subjects with AD and confirm the results of our study.

While previous studies have explored APOE-dependent changes in subjects with AD and MCI, these studies have largely been cross-sectional (Drzezga et al. 2005; Reiman et al. 1996; Roher et al. 2012; Scarmeas et al. 2004). Longitudinal studies are powerful in their ability to assess AD risk over time rather than at a single time point. To our knowledge, our work represents the longest lasting longitudinal study on APOE dependent changes in both MCI and non-demented individuals.

To ensure the reliability of our data and appropriateness of our follow up period, we analyzed the APOE-related AD conversion rates in our data. A Fisher's test for exactness and Chi square test revealed that there is a trend towards APOE

carriers having a greater rate of conversion compared to non-carriers in both the MCI and NC groups. The survival plots in Figure 2 show AD conversion over time is consistent with work by Bonham et al. showing an approximately 60% reduction in survival in APOE carriers compared to 20% for non-carriers in non-demented subjects whose baseline age was between 70 and 80. Further, several studies have supported the dose dependent effects of the APOE genotype on AD progression (Jack et al. 2013; Mosconi, Perani, et al. 2004; Reiman et al. 1996). Taken together, these results qualitatively show that our data exhibit baseline and longitudinal APOE dose dependent effects that are consistent with previous studies. Combined previous and this study, the results indicates that the presence of the APOE allele increases the risk of developing AD concomitantly with an increase in glucose hypometabolism (Mosconi, Nacmias, et al. 2004; Mosconi, Perani, et al. 2004).

In this study, we also assessed the role of APOE ε4 in AD risk without the effects of normal aging. As a result, we found specific regions that showed APOE-related longitudinal decreases in FDG uptake in MCI subjects but not in NC individuals. What's more, we investigated the APOE ε4 related glucose uptake changes using voxelwise analysis and ROI-based analysis. Because one method is data-driven, and other is knowledge-based, these techniques complement each other and using them together increases the reliability and robustness of our study.

When comparing the baseline scan to 24 months follow-up scan, we found two regions in the posterior cerebellum which showed significant longitudinal APOE-related declines in the NC group, and no significant regions in the MCI group. We found no significant regions with APOE dependent declines upon pooling the MCI and NC groups (data not shown). These findings are consistent with work by Lo et. al showing no APOE dependent decreases in FDG-uptake between 0 and 36 months follow-up in NC and MCI individuals with similar baseline ages as our study (p value between NC and MCI baseline ages in our study and Lo et al. was 0.67 and 0.81, respectively) (Lo et al. 2011).

We next considered 24 month scans to the last follow-up period and identified significantly more brain regions that showed an APOE-dependent change over the follow-up period in both the MCI and NC groups. We attempt to explain this seemingly arbitrary finding by using the model proposed by Jack et al. (Jack et al. 2013) in which several core AD biomarkers, including FDG, exist below clinical detection thresholds long before and sometimes after cognitive impairment can be observed in AD patients (Jack et al. 2013). Figure 4 shows a representative graph of FDG measurements from the lateral temporal lobe of subjects with MCI over the follow-up period. The image shows a turning point between APOE carriers and non-carriers at approximately 24 months. The data indicates non-significant smaller differences in FDG SUVR values at earlier time points with a turning point at 24 months by voxelwise and ROI-based analysis as noted in the Discussion section. Taken together, FDG measurements before 24 months may not reliably correlate to Alzheimer's disease progression. By only considering scans 24 months after the first scan, we hypothesize that we have reduced the percentage of subjects with sub threshold biomarker detection levels, and thereby selected the most sensitive time interval to follow Alzheimer's progression using FDG.

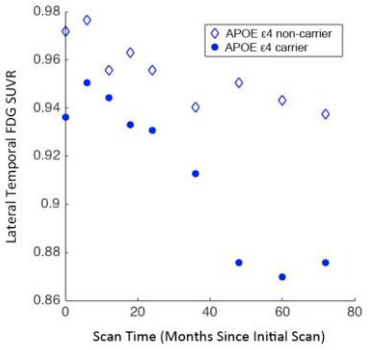

Fig. 4. Longitudinal FDG SUVR of Lateral Temporal values from MCI subjects at baseline over the follow-up period.

5. CONCLUSIONS

We observed greater decline in glucose uptake in APOE ε4 carriers versus non-carriers, consistent with existing research. The superior parietal lobe, inferior temporal gyrus, thalamus, caudate, parahippocampal gyrus, fusiform gyrus and middle temporal gyrus, show APOE ε4 related longitudinal decreases in FDG uptake in individuals with MCI but not NC. Our work represents one of the longest FDG studies of AD, and captures the most appropriate time period to follow AD progression. Our work may improve quantitative FDG imaging as an AD biomarker and help to identify the brain regions most associated with AD progression.

6. ACKNOWLEDGEMENTS

We would like to thank Mr. An Yang, MS and Dr. Lori Beason-Held, PhD (Laboratory of Personality and Cognition, National Institute on Aging, National Institutes of Health) for their technical expertise and advice on statistical and SPM analysis.

7. FUNDING/SUPPORT

The authors have the following interests: 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 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 Neuro Imaging at the University of Southern California. There are no patents, products in development or marketed products to declare.

This work was in part supported by Research Foundation of Peking University First Hospital (2017QN13).

REFERENCES

Chen, Kewei et al. (2011). Characterizing Alzheimer's Disease Using a Hypometabolic Convergence Index. *NeuroImage*, 56(1):52–60.

Chen, Xueqi et al. (2016). Potential Clinical Value of Multiparametric Pet in the Prediction of Alzheimer's Disease Progression. *PLoS ONE*, 11(5):e154406.

Drzezga, a et al. (2005). Cerebral Glucose Metabolism in Patients with AD and Different APOE Genotypes. *Neurology*, 64:102-7.

Farrer, L. A. et al. (1997). Effects of Age, Sex, and Ethnicity on the Association Between Apolipoprotein E Genotype and Alzheimer Disease: A Meta-Analysis. *JAMA: The Journal of the American Medical Association*, 278(16):1349–56.

Jack, Clifford R. et al. (2013). Update on Hypothetical Model of Alzheimer's Disease Biomarkers. *Lancet neurology*, 12(2):207–16.

Liu, C. et al. (2013). Apolipoprotein E and Alzheimer Disease: Risk, Mechanisms and Therapy. *Nature reviews. Neurology,* 9(2):106–18.

Lo, Raymond Y. et al. (2011). Longitudinal Change of Biomarkers in Cognitive Decline. *Archives of neurology,* 68(10):1257–66.

Madhav, T. et al. (2010). APOE (epsilon)4 Genotype and Longitudinal Changes in Cerebral Blood Flow in Normal Aging. *Archives of neurology,* 67(1):93–98.

Mosconi, L., B. et al. (2004). Brain Metabolic Decreases Related to the Dose of the ApoE e4 Allele in Alzheimer's Disease. *Journal of neurology, neurosurgery, and psychiatry,* 75(3):370–76.

Mosconi, L., D. et al. (2004). MCI Conversion to Dementia and the APOE Genotype: A Prediction Study with FDG-PET. *Neurology,* 63:2332–40.

Mosconi, Lisa. et al. (2010). Pre-Clinical Detection of Alzheimer's Disease Using FDG-PET, with or without Amyloid Imaging. *Journal of Alzheimer's Disease,* 20(3):843–54.

Reiman, E. M. et al. (1996). Preclinical Evidence Of Alzheimers Disease In Persons Homozygous For the ε-4 Allele For Apolipoprotein E. *New England Journal of Medicine* 334(12):752–58.

Roher, Alex. et al. (2012). Cerebral Blood Flow in Alzheimer's Disease. *Vascular Health and Risk Management*, 42(10):599-611.

Rosén, C. et al. (2013). Fluid Biomarkers in Alzheimer's Disease - Current Concepts. *Mol Neurodegener*, 8(1):20.

Scarmeas, N. et al. (2004). APOE-Dependent PET Patterns of Brain Activation in Alzheimer Disease. *Neurology*, 63(5):913–15.

Small, G. W. et al. (2000). Cerebral Metabolic and Cognitive Decline in Persons at Genetic Risk for Alzheimer's Disease. *Proceedings of the National Academy of Sciences of the United States of America*, 97(11):6037–42.

Thambisetty, et al. (2010). APOE epsilon4 Genotype and Longitudinal Changes in Cerebral Blood Flow in Normal Aging. *Archives of neurology*, 67(1):93–98.

Table 1. ROIs with Greater Decrease of FDG SUVR analysis in APOE ε4 Carriers versus Non-Carriers

Region	NC group	MCI group
baseline vs. last follow-up		Parietal (p=0.029)
		Caudate (p=0.018)
24 months vs. last follow-up	Prefrontal (p=0.032)	Lateral Temporal (p=0.045)
	Superior Frontal (p=0.041)	Parietal (p=0.001)
	Lateral Temporal (p=0.022)	Caudate (p=0.013)