IC-P-096 ALTERED FUNCTIONAL BRAIN NETWORK IN COGNITIVELY NORMAL ELDERLY WITH GENETIC HIGH RISK FOR ALZHEIMER'S DISEASE: GRAPH-THEORETICAL ANALYSIS OF BRAIN GLUCOSE METABOLISM

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Background: Graph theoretical approach provides mathematical and conceptual framework for understanding brain as a complex network. Nevertheless, this approach was not yet applied to understand brain metabolic network in cognitively normal (CN) individuals and its alterations in the individuals with genetic high risk for Alzheimer disease (AD). This study aimed to investigate the properties of brain metabolic network in CN elderly people and their changes in the individuals with genetic risk for AD, i.e., apolipoprotein E (APOE) E 4 allele, using graph theoretical analysis of brain glucose metabolism. **Methods:** We included 94 CN elderly, aged 55-84 years. Among the participants, 28 were APOE E 4 carriers and 58 were non-carriers. The remaining 8 individuals did not received APOE genotyping. All the subjects underwent clinical evaluation and resting [18 F] fluorodeoxyglucose positron emission tomography (FDG-PET) scan. All brain regions except cerebellum were parcellated into 90 regions of interest (ROIs) using the automated anatomical labeling (AAL) template. Brain metabolic networks were constructed from correlation matrices of the 90 ROIs and analyzed using graph theoretical approaches. Network parameters were calculated for total CN group and each subgroup according to APOE genotype (APOE E4 carriers vs. non-carriers) and estimated repeatedly over a wide range of sparsity ($1\% \leq S \leq 40\%$). **Results:** Small world properties were observed in the whole CN group. Subgroup analysis revealed that APOE E4 carriers had altered small world properties, characterized by lower clustering coefficient and shorter path length compared with APOE E4 non-carriers. The result suggests overall increase of randomness in APOE E4 carriers' brain metabolic network. For hubs, identified by betweenness centrality (b i), APOE E4 carriers showed significant b i decrease in the right hippocampus compared with non-carriers (b i = 0.14 for carriers, b i = 2.23 for non-carriers). In contrast, APOE E4 carriers showed significant b i increase in the bilateral precuneus and several regions in occipital and temporal lobes. **Conclusions:** Our results first indicate genetic vulnerability for AD probably alter functional brain network even before clinical symptoms emerge. Graph theoretical analysis of brain glucose metabolism seems to be a useful approach to detect the early subtle change in brain network related to AD process.

IC-P-097 INFLUENCE OF APOE-ε4 GENOTYPE ON GLOBAL AND REGIONAL Aβ DEPOSITION: RESULTS FROM THREE WW-ADNI [C-11]PIB DATA STUDIES

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Background: Apolipoprotein E (APOE) e 4 and e 2 allele has been implicated as positive and negative risk factors for Alzheimer's disease (AD), respectively. However, their detailed pathophysiological roles are not known. In this study, we evaluated the influence of APOE genotype on the global and the regional brain accumulation of 11 C-Pittsburgh compound B (PiB) in three nation-wide prospective imaging studies of AD; Alzheimer's Disease Neuroimaging Initiative (US-ADNI), Austrarian Imaging Biomarker and Lifestyle (AIBL), and Japanese Alzheimer's Disease Neuroimaging Initiative (J-ADNI). **Methods:** We analyzed a total of 386 baseline 11 C-PiB scan data acquired 50-70 min post-injection in all the studies. The PET images were co-registered to individual MRI data, and automated VOI analysis were performed using DARTEL template, standard set of volumes of interest, and cerebrospinal fluid volume correction. The regional (precuneus, frontal, temporal and parietal cortices) uptake was evaluated in reference to that of the cerebellum. The mean cortical uptake (mcSUVR) was regarded as the representative value of individual global cortical amyloid deposition. The cut-off mcSUVR value for PiB-positivity was set at 1.5 for all the studies. Among all the studies, the number of subjects in each APOE genotype with PiB positive or negative (PiB+/PiB-) were; e 2 e 2 (0/1), e 2 e 3 (4/20), e 2 e 4 (7/3), e 3 e 3 (71/106), e 3 e 4 (110/31) and e 4 e 4 (14/19). **Results:** In the PiB-positive subjects, 11 C-PiB uptake level was significantly elevated ($P < 0.001$) in all the regions and the whole brain in e 4 carrier subjects with apparent gene dose effect. On the other hand, the regional 11 C-PiB uptake in precuneus solely showed significant reduction ($P<0.05$) in e 2 carrier subjects. **Conclusions:** These results suggest that ApoE e 4 allele has a strong effect facilitating Amyloid β (Aβ) deposition in all the brain regions without regional preferences. On the other hand, APOE e 2 allele seems to have some regional weighted effect to reduce A β deposition especially in the precuneus. Further studies are required to examine the relationship between the spatial distribution of A β deposition and APOE genotype and their role on AD pathogenesis.

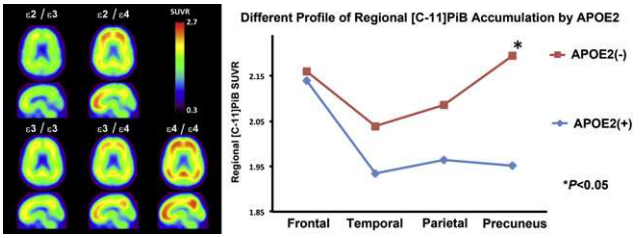

Figure. [C-11]PiB Accumulation by APOE Genotype

IC-P-098 THE ROLE OF APOE-ε4 GENOTYPE IN EARLY MILD COGNITIVE IMPAIRMENT (EMCI): PRELIMINARY RESULTS FROM ADNI-2

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Background: Apolipoprotein E (APOE) genotype is the most significant genetic variant associated with late-onset Alzheimer's disease (AD) susceptibility and pathological features [1]. However, the role of APOE in very early prodromal stages of AD is not well understood. The new ADNI category of early amnestic mild cognitive impairment

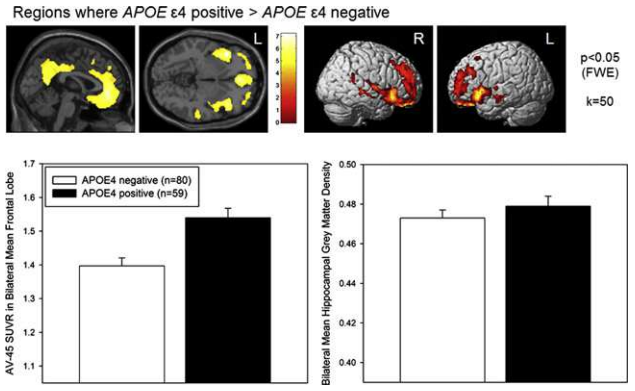

Figure 1. (A) Effect of *APOE* Genotype on Amyloid Deposition. (B) Frontal Amyloid by *APOE* Genotype. (C) Hippocampal Atrophy by *APOE* Genotype.

(E-MCI) provides an opportunity to evaluate the role of APOE E4 genotype on psychometric performance, amyloid deposition and neurodegeneration in patients with very mild clinical impairments. **Methods:** Baseline pre-processed AV-45 PET scans [2], 3T MRI scans [3], APOE genotype [4] and other quantitative phenotypes were downloaded from the ADNI website. Only participants categorized as E-MCI (n = 139) at baseline from ADNI-GO/2 were included. MRI scans were processed using VBM, as previously described [5]. AV-45 scans were co-registered to the concurrent MRI and normalized to MNI space using parameters generated from MRI segmentation. Differences between APOE E4 allele positive and negative participants in AV-45 standardized uptake on a voxel-wise basis were assessed using a two-sample t-test using SPM8. Region of interest (ROI) data was extracted from MRI and AV-45 scans using MarsBaR. Neuropsychological performance, cognitive complaints, and ROI data were compared between E4 positive and negative participants using independent-samples t-tests (SPSS 19.0). **Results:** Approximately 42% of the E-MCI participants (n = 139) were APOE E4 positive (n = 59; 2 E2E4, 48 E3E4, 9 E4E4; Table 1). The E4 positive E-MCI group showed lower performance on memory and global cognitive measures, but a trend toward fewer cognitive complaints, than APOE E4 negative participants (n = 80; 9 E2E3, 71 E3E3). On AV-45 PET, E4 was associated with increased amyloid deposition, particularly in frontal and medial parietal lobar regions (Figure 1A; $P < 0.05$ FWE, k = 50). Similarly, ROI analyses indicated greater amyloid deposition in the frontal lobes of E4 positive E-MCI participants (Figure 1B; $P < 0.001$). By contrast, the presence of E4 was not associated with greater hippocampal atrophy in this initial sample of E-MCI participants (Figure 1C). **Conclusions:** In E-MCI, APOE E4 genotypes are associated with greater amyloid deposition and cognitive changes, but not hippocampal neurodegeneration. References: [1] Corder (1993). [2] Jagust (2010). [3] Jack (2010). [4] Saykin (2010). [5] Risacher (2009).

Table 1
Demographics and neuropsychological test performance (Mean (SE))

	ε4 negative	ε4 positive	*P*-value
n	80	59	
Age (years)	71.97 (0.86)	70.81 (1.00)	ns
Gender (M, F)	39, 41	37, 22	ns
Education (years)	15.96 (0.30)	15.73 (0.35)	ns
Handedness (R, L)	71, 9	55, 4	ns
CDR-SB[a]	1.11 (0.08)	1.38 (0.09)	0.022
ADAS-Cog Total[a,b]	10.95 (0.53)	13.79 (0.61)	0.0007
RAVLT Total[a]	41.76 (1.03)	37.54 (1.20)	0.009
RAVLT Delayed Recall[a]	6.97 (0.42)	5.23 (0.49)	0.008
Trail-Making B-A[a,c]	53.90 (4.86)	69.38 (5.65)	0.042
ECog Patient Total	20.41 (1.08)	17.88 (1.25)	ns
ECog Informant Total	16.03 (1.11)	14.80 (1.29)	ns
ECog-Mem Patient Total	5.95 (0.23)	5.83 (0.27)	ns
ECog-Mem Informant Total	4.94 (0.28)	4.78 (0.33)	ns
ECog-Lang Patient Total	5.23 (0.30)	4.46 (0.35)	ns
ECog-Lang Informant Total	3.36 (0.33)	3.27 (0.38)	ns
ECog-VS Patient Total	2.58 (0.27)	1.85 (0.32)	ns
ECog-VS Informant Total	1.95 (0.24)	1.39 (0.28)	ns
ECog-Exec Patient Total	6.66 (0.48)	5.75 (0.55)	n
ECog-Exec Informant Total	5.78 (0.50)	5.36 (0.58)	ns

(*Continued*)

[a]Adjusted for age, gender, education, and handedness
[b]Missing data for 1 ε4 negative participant
[c]Missing data for 3 participants (2 ε4 negative, 1 ε4 positive)

IC-P-099 ELEVATED PIB PRECEDES DEMENTIA IN AUTOSOMAL DOMINANT ALZHEIMER'S DISEASE: PIB, FDG AND ATROPHY IN THE DIAN COHORT

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Background: DIAN (Dominantly Inherited Alzheimer's Network) is an international longitudinal study of autosomal dominant Alzheimer's Disease (ADAD). In addition to clinical, cognitive and psychometric testing, participants undergo serial multi-modal imaging. **Methods:** 120 participants representing a mix of non-carrier and carriers in both the presymptomatic and symptomatic stages of AD underwent PIB, FDG PET and MRI. Cohorts were determined based on genetic status, dementia severity (Clinical Dementia Rating, CDR), and estimated time to dementia onset (TDO, based on parental age of onset). All imaging exams were transformed and processed in a common atlas