IC-P-018 FUNCTIONAL NETWORK ANALYSIS OF FLORBETAPIR-LOW AND FLORBETAPIR-HIGH ADNI MCI SUBJECTS

Felix Carbonell[1], Arnaud Charil[1], Andrew Reid[2], Alex Zijdenbos[1], Alan Evans[1], Barry Bedell[1], *[1]Biospective Inc., Montreal, Quebec, Canada; [2]Montreal Neurological Institute, Quebec, Canada.*

Background: Structural and functional brain network analysis can provide unique insights into the natural evolution of Alzheimer's disease, as well as facilitate the assessment of therapeutic intervention. In order to elucidate the effect of β-amyloid deposition on brain networks at the early disease stage, we have performed a graph theory-based analysis of functional brain networks derived from FDG positron emission tomography (PET) images of florbetapir-low and florbetapir-high MCI subjects in the Alzheimer's Disease Neuroimaging Initiative (ADNI) study. **Methods:** T1-weighted MRI, [18F]florbetapir (AV-45) PET, and [18F]FDG PET images were obtained from ADNI-GO/-2 study subjects classified with mild cognitive impairment (MCI). Standardized uptake value ratio (SUVR) images for florbetpir and FDG PET were generated using our fully-automated PIANO TM pipeline. All PET volumes were registered to a customized MRI template in MNI stereotaxic space. Subjects were classified into florbetapir-low and florbetapir-high groups using lower and upper SUVR thresholds based on a composite ROI. An ROI-based FDG SUVR correlation matrix was then constructed for each group in which SUVR values for each pair of ROIs were correlated across subjects. A Bonferroni correlation threshold was employed to binarize the correlation matrices, and graph theory-based measures, including global, local, and integrated regional efficiencies, were computed for both groups. **Results:** The florbetapir-low group possessed more hubs and a more densely connected network compared to the florbetapir-high group. The number of intra-lobar connections within the frontal lobe and long-range frontal-to-parietal connections, especially nodes of the default-mode network (DMN), were reduced in the florbetapir-high group. The florbetapir-high group also demonstrated lower global, local, and integrated regional efficiencies relative to the florbetapir-low group. **Conclusions:** We have employed graph theory analysis to examine the effects of β-amyloid plaque burden on large-scale brain network properties in MCI subjects. Our analysis identified reduced connectivity and lower network efficiency in subjects with higher amyloid load. While this study examined functional networks based on glucose utilization, future studies will evaluate similar network properties derived from resting-state BOLD and/or ASL perfusion MRI data. Based on this study, network analysis of functional imaging data may serve as a sensitive imaging biomarker for the assessment of therapeutic intervention in early disease studies.

IC-P-019 COMBINATION OF GRAY MATTER DENSITY AND GLOBAL COGNITIVE INFORMATION AS A BETTER PREDICTOR OF THE CONVERSION TO ALZHEIMER'S DISEASE IN MILD COGNITIVE IMPAIRMENT: A TWO-YEAR FOLLOW-UP STUDY

Bo Kyung Sohn[1], Dong Young Lee[2], Eun Hyun Seo[2], Il Han Choo[2], Young Min Choe[2], Jae-Min Shon[2], Jae-Hwa Bak[3], Jong Inn Woo[2], *[1]Seoul National University, Seoul, South Korea; [2]Seoul National University Hospital, Seoul, South Korea; [3]Seoul National University Hospital, Seoul, South Korea.*

Background: This study aimed to investigate Alzheimer' disease (AD) prediction ability of clinical assessment, neuropsychological tests, apolipoprotein E (ApoE) genotyping, [18 F] fluorodeoxyglucose positron emission tomography (FDG-PET), structural MRI, and diffusion tensor imaging (DTI) at baseline and to search the most effective model to predict Alzheimer's disease (AD) in mild cognitive impairment (MCI) patients after a two-year follow-up period. **Methods:** Thirty two elderly subjects with MCI and 26 cognitively normal (CN) elderly individuals were evaluated at baseline with a sum of boxes score of clinical dementia rating (CDR-SOB), eight CERAD neuropsychological tests, the ApoE genotyping, FDG-PET, MRI, and DTI, and followed up annually for 2 years. Voxel-based statistical comparisons of baseline FDG-PET, MRI, DTI data were performed between AD converted MCI (MCIc) and non-converted MCI (MCInc). A series of logistic regression analyses were conducted to examine the AD prediction ability of each assessment modality alone and various combinations of modalities. **Results:** Of MCI patients, 12 (37.5%) were converted to clinically evident AD (MCIc) and 20 (62.5%) were still in the MCI state (MCInc) after the 2-year follow-up. Compared with MCInc, MCIc showed reduced regional cerebral glucose metabolism (rCMglc) in the right inferior parietal lobule, right cingulate gyrus and left angular gyrus at baseline, reduced gray matter (GM) density in right inferior parietal lobule, lower CDR-SOB score, and lower mini-mental state examination (MMSE) score. The ApoE genotyping and CERAD neuropsychological tests except MMSE, and fractional anisotropy (FA) and mean diffusivity (MD) values derived from DTI were not significantly different between MCIc and MCInc. In terms of AD prediction after two-years in MCI, logistic regression analyses showed that the combination model including right inferior parietal lobule density on MRI and MMSE score (accuracy: 87.5%) was significantly better than any other models. **Conclusions:** The combination of GM density information on MRI and global cognitive score is probably the most cost-effective model to predict Alzheimer's disease (AD) in mild cognitive impairment (MCI) patients after a two-year follow-up period.

IC-P-020 A VOXEL-BASED MORPHOMETRY STUDY OF VOLUMETRIC MRI IN FAMILIAL ALZHEIMER'S DISEASE

David Cash[1], Gerard Ridgway[2], Natalie Ryan[2], Kirsi Kinnunen[3], Tom Yeatman[4], Ian Malone[1], Tammie Benzinger[5], Robert Koeppe[6], Clifford Jack Jr.[7], Marc Raichle[5], Daniel Marcus[8], John Ringman[9], Paul Thompson[9], Andrew Saykin[10], Stephen Salloway[11], Stephen Correia[11], Keith Johnson[12], Reisa Sperling[13], Peter Schofield[14], Colin Masters[15], Christopher Rowe[16], Victor Villemagne[16], Ralph Martins[17], Adam Brickman[18], Richard Mayeux[19], Michael Weiner[20], Randall Bateman[5], Alison Goate[21], Anne Fagan[5], Chengjie Xiong[5], Nigel Cairns[21], Virginia Buckles[5], Krista Moulder[5], John Morris[5], Martin Rossor[1], Sebastien Ourselin[1], Nick Fox[1], *[1]University College of London, London, United Kingdom; [2]UCL Institute of Neurology, London, United Kingdom; [3]University College of London, Institute of Neurology, London, United Kingdom; [4]University College of London, London, United Kingdom; [5]Washington University School of Medicine, St. Louis, Missouri, United States; [6]University of Michigan at Ann Arbor, Ann Arbor, Michigan, United States; [7]Mayo Clinic, Rochester, Minnesota, United States; [8]Washington University School of Medicine, St. Louis, Missouri, United States; [9]UCLA, Los Angeles, California, United States; [10]Indiana University, Indianapolis, Indiana, United States; [11]Brown University, Providence, Rhode Island, United States; [12]MGH HMS, Boston, Massachusetts, United States; [13]Harvard Medical School, Boston, Massachusetts, United States; [14]Neuroscience Research Australia, Randwick-Sydney, Australia; [15]University of Melbourne, Melbourne, Victoria, Australia; [16]Austin Health, Melbourne, Australia; [17]Edith Cowan University, Perth, Australia; [18]Columbia University, New York, New York, United States; [19]Columbia University Medical Center, New York, New York, United States; [20]University of California, San Francisco, San Francisco, California, United States; [21]Washington University School of Medicine, St. Louis, Missouri, United States.*

Background: DIAN (Dominantly Inherited Alzheimer's Network) is an international longitudinal study of autosomal dominant Alzheimer's disease that involves serial clinical, imaging and biomarker studies of individuals at risk of disease and those already mildly affected. Understanding the patterns of atrophy associated with the disease will be important for studies and trials tracking atrophy progression in these cohorts. **Methods:** 158 participants from the DIAN cohort were included of whom 55 were non carriers (NC); 59 were asymptomatic carriers (aMut+) with a Clinical Dementia Rating (CDR) of 0; and 44 were symptomatic carriers (sMut+) with CDR >0. Voxel based morphometry (VBM)

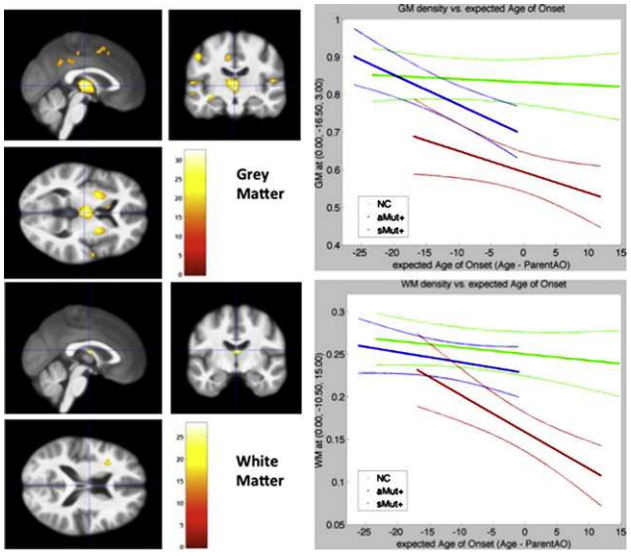

Figure. Summary of VBM study. Left column: centered on a significant cluster in the thalamus. A significant cluster in the putamen can also be seen. Right: significant cluster in the fornix. The plots below are the linear fit (with 95% confidence interval) of the tissue densities with respect to expected age at onset.

of baseline MR imaging was used to investigate differences in grey matter (GM) and white matter (WM) between the different groups. Tissue segmentation and spatial normalization of volumetric T1-weighted images were performed using the VBM8 toolbox of SPM8. One participant was excluded due to severe WM hyperintensities. Images were smoothed using a 6mm full-width-half-maximum Gaussian kernel. Statistical parametric maps were generated of the GM and WM differences between groups, controlling for total intracranial volume (TIV), gender, acquisition site, and APOE genotype. An interaction term between group and the expected age of onset (current age - parental age of onset) was included. **Results:** Significant clusters ($P<0.05$ Family-Wise Error corrected) in the GM were observed between groups in the thalamus, precuneus, putamen, and amygdala. Most clusters were primarily driven by differences between the sMut+ and NC group (see Figure). No significant clusters were observed between the aMut+ and NC groups. There were also clusters in the parahippocampal/hippocampal regions. WM differences between groups were observed in the fornix superior to the thalamus, the cingulum inferiorly adjacent to the hippocampus, the splenium adjacent to the cingulate and areas adjacent to the precuneus. **Conclusions:** Symptomatic subjects show widespread differences in GM volume including deep grey structures (e.g. thalamus and putamen) and the precuneus; notable white matter changes included the fornix and the cingulum. The deep grey changes are of interest as PIB PET findings suggest early amyloid deposition in these structures.

IC-P-021 RATES OF BRAIN AND HIPPOCAMPAL ATROPHY IN PRESYMPTOMATIC FAMILIAL ALZHEIMER'S DISEASE: ACCELERATION AND MUTATION EFFECTS

David Cash[1], Yuying Liang[1], Kelvin Leung[2], Natalie Ryan[2], Marc Modat[1], Manuel Cardoso[3], Tom Yeatman[1], Sebastian Crutch[1], Felix Woodward[1], Ian Malone[1], Jonathan Bartlett[4], Kirsi Kinnunen[5], Martin Rossor[1], Sebastien Ourselin[1], Nick Fox[1], *[1]University College of London, London, United Kingdom; [2]UCL Institute of Neurology, London, United Kingdom; [3]University College of London, London, United Kingdom; [4]London School of Hygiene and Tropical Medicine, London, United Kingdom; [5]University College of London, Institute of Neurology, London, United Kingdom.*

Background: Subjects at risk of familial Alzheimer's Disease (FAD) offer the best chance to observe the earliest effects of the disease and would be candidates for presymptomatic trials. Currently there is relatively little longitudinal data available on subjects in the earliest stages of disease. Here, we analyze the atrophy rates of key structures in a local longitudinal FAD cohort which has been followed for up to two decades. **Methods:** 36 individuals (24 from PS1 families and 12 from APP families, mean (SD) age 46.3 (8.6) years) with FAD or at risk were recruited into the study. Each had 2 to 11 MRI scans approximately annually and were followed for up to 16 years. For each subject the scan at first onset of symptoms was identified. Forty-four age- and sex-matched control subjects (mean [sd] age 48.4 [11.2] years) were scanned twice on average 1.3 [0.6] years apart. Brain, ventricles, and hippocampi were segmented using automated techniques. Linear mixed models were fitted to estimate atrophy rates according to time to symptom onset and to test for acceleration in rates. The models also adjusted for TIV and scanner. **Results:** At time of symptom onset, mutation carriers already had significantly increased rates of atrophy for all structures compared to controls (see Table). Whole brain atrophy rates at symptom onset were similar in the two mutation groups (APP 1.51%/year (95% CI 0.92, 2.10), PS1 1.25% (0.76, 1.74)), but there was evidence of greater acceleration in rates in PS1 subjects ($P<0.001$). Hippocampal atrophy was greater at symptom onset in APP (2.17% (1.68, 2.65)) compared to PS1 (1.13% (0.70, 1.56)), with evidence of acceleration in rates in both groups. Rates of ventricular enlargement were similar in APP (13.5% (9.1, 18.1)) and PS1 (11.6% (7.9, 15.4)), but there was evidence of greater acceleration in PS1 ($P = 0.006$). **Conclusions:** Increased atrophy rates,

Table
Atrophy and acceleration rates (with 95% confidence intervals) for controls and subjects with FAD, grouped by mutation status.

		Controls (n = 44)	APP (n = 12)	PS1 (n = 24)
Demographics	# of scans	88	56	93
	Male %	20 (45.5)	6 (50)	10 (41.7)
	Age at First Scan	48.4 (11.2)	51.3 (5.5)	43.8 (8.9)
Whole Brain	Atrophy rate (%/year) at symptom onset	-0.01 (-0.27, 0.25)	1.51 (0.92, 2.10)	1.25 (0.76, 1.74)
	Acceleration of atrophy rate (%/year^2)	-	-0.03 (-0.09, 0.03)	0.17 (0.09, 0.25)$^+$
	p-value for acceleration	-	0.40	<0.001
Ventricles	Atrophy rate (%/year) at symptom onset	0.2 (-1.9, 2.3)	13.5 (9.1, 18.1)	11.6 (7.9, 15.4)
	Acceleration of atrophy rate (%/year^2)	-	0.41 (0.13, 0.69)	1.14 (0.69, 1.59)$^+$
	p-value for acceleration	-	0.004	<0.001
Hippocampi (L+R averaged)	Atrophy rate (%/year) at symptom onset	-0.09 (-0.40, 0.23)	2.17 (1.68, 2.65)*	1.13 (0.70, 1.56)
	Acceleration of atrophy rate (%/year^2)	-	0.23 (0.13, 0.32)	0.20 (0.08, 0.31)
	p-value for acceleration	-	<0.001	0.001

In all three structures the atrophy rate at symptom onset was significantly higher than controls. The p-values listed test whether the value for acceleration is non-zero. A * indicates that there is strong evidence that hippocampal atrophy rates at symptom onset differ between APP and PS1 ($P = 0.001$). A $^+$ indicates that there is evidence that the acceleration rates of whole brain ($P<0.001$) and ventricular atrophy ($P = 0.006$) differ between APP and PS1.