IC-P-115 ASSOCIATION BETWEEN CORTICAL THICKNESS AND CSF BIOMARKERS IN MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE

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Background: The dynamic biomarker hypothesis predicts that fluid biomarker abnormalities precede brain morphological changes observed in AD by many years. However, the link between early CSF abnormalities and late structural changes remains under debate. Here we investigated the association between regional cortical thinning (CT) measured by Magnetic Resonance Imaging (MRI) and brain amyloidosis (measured by CSF Aβ 1-42 concentrations), or tau hyperphosphorylation (tau 181; p-tau) in Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI) patients. We test the hypothesis that the association between cortical thinning, amyloidosis or tau hyperphosphorylation depends on cortical regions and clinical stages of AD. **Methods:** T1-weighed MRIs and associated CSF markers from individuals with mild cognitive impairment (MCI; 16), Alzheimer Disease (AD; n=7) and age-matched cognitively normal subjects (CN; n=8) were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort. Cortical surface reconstruction and group registration were generated using Freesurfer. A general linear model was used to conduct regressions between CSF markers and cortical thickness. **Results:** Correlation analyses in the MCI group showed a positive correlation between CT and Aβ 1-42 measures predominantly in the temporo-parietal regions, namely the precuneus (peak r=0.67; p<0.01) and the fusiform (peak r=0.85; p<0.0001). Similar but smaller effects were present in AD, with additional clusters in the frontal cortex (peak r=0.94; p=0.0001). In both MCI and AD groups, significant clusters of negative correlations between CT and p-tau were mainly found in medio-temporal and dorso-lateral prefrontal areas. In the CN group, no relationship was observed between cortical thickness and either CSF biomarkers. **Conclusions:** Although limited by sample sizes, our results suggest a posterior-anterior gradient of structural vulnerability to A b 1-42. Alternatively, weaker temporo-parietal effect between CT and Aβ 1-42 in AD relative to MCI, likely results from a ceiling effect of Aβ 1-42 levels in the AD group. Conversely, a frontal effect can only be found in the AD group, which possibly corresponds to a later stage of Aβ 1-42 -driven neurodegeneration.

IC-P-116 BASELINE OR PROGRESSION? BIOMARKERS PREDICTIVE OF MEMORY DECLINE

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Background: It is not known which component of commonly employed Alzheimer's disease (AD) biomarkers –baseline value or progression–is a better predictor of cognitive decline. We examined how much of individual

Table 1
Proportion of memory decline (variability in longitudinal slope) explained by each biomarker: baseline and change values Itthickness: inferior temporal thickness Tpthickness: temporal pole thickness

	Normal Group		Among MCI*		Among AD	
Biomaker _bl: baseline values _progression: changes	% of variability explained by biomarkers	Standardized effect size	% of variability explained by biomarkers	Standardized effect size	% of variability explained by biomarkers	Standardized effect size
ttau_bl	-7.00%	0.02	-0.40%	-0.01	-7.90%	-0.19
ttau_progression	-7.80%	-0.02	-1.50%	-0.02	-17.80%	-0.08
$Abeta_{42}$_bl	-5.90%	0.01	4.40%	0.08	-8.60%	-0.05
$Abeta_{42}$_progression	-13.40%	0.02	-0.40%	0.05	6.60%	-0.04
FDG-PET_bl	-0.50%	0.04	12.50%	0.09	29.10%	0.17
FDG-PET_progression	2.80%	0.05	14.60%	0.05	39.40%	0.12
Wmh/icv_bl	-4.20%	0.04	0.70%	-0.02	-4.80%	0.09
Wmh/icv_progression	-2.20%	-0.04	-0.20%	0.01	2.80%	0.11
Hpcv/icv_bl	-0.40%	0.04	9.60%	0.06	3.40%	-0.14
Hpcv/icv_progression	-4.40%	0	15.60%	0.06	2.60%	0.12
Ventricles/icv_bl	-0.70%	-0.01	8.60%	-0.07	-0.30%	0
Ventricles/icv_progression	-5.50%	-0.02	27.60%	-0.08	68.90%	-0.19
wbrain/icv_bl	0.00%	0.02	3.20%	0.05	-4.50%	0.04
wbrain/icv_progression	-3.30%	0.01	16.60%	0.06	28.90%	0.14
mtthickness/icv_bl	-3.60%	-0.01	5.60%	0.08	7.20%	0.09
mtthickness/icv_progression	-1.10%	0.03	22.50%	0.08	51.40%	0.15
itthickness/icv_bl	-2.40%	-0.01	4.80%	0.08	8.80%	0.05
itthickness/icv_progression	1.60%	0.03	28.30%	0.09	73.00%	0.19

Brain volumes and cortical thickness were divided by intracranial volume. Controlling for age at baseline, sex, education, apoe 4 allele (at least one vs. none) and practice effects (an indicator of before 6 months assessment vs. at/after 6 months assessment for memory composite outcome: 6 months was used as a cutoff based on the visual inspection of trajectory and the improvement in model fit). *: to capture the change in diagnosis from MCI to AD during the follow-up, an indicator variable (before MCI coded as 0, after MCI coded as 1) was included as a control variable to capture the shift in slopes in cognitive decline.

The table can be read as follows: For example, among MCI subjects, one standard deviation larger expansion in icv-adjusted ventricular volume (ventricles/icv_progression) is associated with 0.08 further decline in memory scores each year (slope effect: -0.08) and the progression explains 27.6% of variability in cognitive decline, while baseline explains only 8.6% of variability in cognitive decline.

differences in cognitive decline (variability in longitudinal slope) measured by neuropsychological tests can be explained by changes/progression of biomarkers as opposed to their baseline values at each cognitive stage (normal, MCI, mild AD). **Methods:** 526 subjects in the Alzheimer's Disease Neuroimaging Initiative (ADNI) with valid data in all of our variables of interest were used in this study. The primary clinical outcome is the cognitive composite score tapping the memory domain. Baseline values and progression in the following biomarkers were examined in their association with trajectory of the cognitive outcome: MRI total brain, hippocampal, ventricular, WMH volumes, ROI cortical thickness (medial and inferior temporal thickness), FDG-PET summary score (n=260) and CSF p-tau, t-tau and abeta42 (n=271). First, individual-specific slope (i.e., random component) of the longitudinal trajectory of each biomarker was estimated using mixed effects models, controlling for age, sex, education, practice effects, apoe 4 allele and changes in diagnosis. Then these estimates and observed baseline values were used as predictors of cognitive decline using mixed effects models. Variability in cognitive decline (i.e., individual differences in slopes) explained by the subject-specific baseline biomarker values was compared with that explained by the progression. **Results:** Even among the normal subjects where cognitive decline is minimal, progression in FDG-PET (but not baseline) explained the variability in memory decline. Also progression explained variability in memory decline more than the baseline values in most biomarkers; the proportion of variability explained ranged from 14.6% (changes in FDT-PET) to 28.3% (changes in inferior temporal thickness) among the MCI subjects. Among AD subjects, an even higher proportion was explained by the progression: 39.4% (changes in FDG-PET), 51.4% (changes in medial temporal thickness), 68.9% (ventricular expansion), 73.0% (changes in inferior temporal thickness). **Conclusions:** Progression in biomarkers is more important than baseline values in most biomarkers in predicting cognitive decline. This has important implications for clinical trials targeted to modify AD biomarkers, as well as for prognosis and prediction of clinical outcomes.

IC-P-117 CHARACTERIZATION OF REGIONAL CEREBRAL BLOOD FLOW IN MILD COGNITIVE IMPAIRMENT AND OLDER ADULTS WITH COGNITIVE COMPLAINTS

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Background: Characterization of CBF change patterns in individuals progressing from cognitively normal to pre-MCI, MCI, and eventually AD will greatly enhance the understanding of neural and vascular mechanisms underpinning pathophysiological progression. Arterial spin labeling (ASL) MRI utilizes magnetically labeled blood water as an endogenous tracer for non-invasive quantification of brain perfusion. Recent studies have explored ASL in MCI and AD, yet results appear inconsistent (Alsop 2010). Our previous studies using other neuroimaging methods have suggested the feasibility of earlier detection in euthymic older adults with marked cognitive complaints (CC) but normal neuropsychological test performance (Saykin 2006, Wang 2012). This study aimed to characterize regional cerebral blood flow (rCBF) in CC, MCI and healthy controls (HC) using ASL. **Methods:** Pulsed MRI perfusion was performed in 16 HC, 15 CC and 15 MCI participants at 3T (Siemens Trio) using the Q2TIPS pulsed ASL (PASL) sequence. A T1-weighted MPRAGE was acquired using the ADNI protocol. Individual quantitative rCBF maps were generated from PASL images (Wang 2011). The general linear model was utilized in SPM8 for voxel-wise group comparison. The BPM toolkit was applied to control for potential atrophy (Casanova 2007). Mean rCBF in individual regions-of-interest (ROIs) derived from segmentation using FreeSurfer 5.1 were further analyzed. Participants underwent comprehensive cognitive and clinical assessment, including evaluation of memory and executive functioning. **Results:** Compared to HC and CC, MCI participants showed reduced rCBF in bilateral temporal regions. CC participants showed increased rCBF along midline default mode network regions, including posterior cingulate cortex (PCC), in comparison with HC ($p<0.005$). Using age and sex as covariates, ROI analyses indicated significant positive correlations between dementia severity (CDR) and rCBF in right hippocampus, parahippocampal gyrus, inferior parietal lobules, and left inferior temporal lobe ($r=0.316$ to 0.478, $p<0.05$). rCBF in PCC negatively correlated with neuropsychological performance (CVLT and WCST; $r=-0.328$ to -0.461, $p<0.05$). **Conclusions:** Our results suggest a nonlinear relationship between rCBF and disease progression in prodromal AD. While hypoperfusion in MCI is consistent with hypometabolism reported with FDG-PET, increased rCBF in the CC group may have implications for pathophysiology and the role of compensatory responses to neurodegeneration in prodromal stages.

IC-P-118 ALTERED CONNECTOME MAPPING IN MILD COGNITIVE IMPAIRMENT AND OLDER ADULTS WITH COGNITIVE COMPLAINTS

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Background: There is increasing evidence showing that cognitive decline is associated with aberrant topological organization of the brain network in AD (Lo 2010); however, the alteration of large-scale brain networks in the preclinical stages of AD remains largely unknown. Our previous studies have suggested the feasibility of earlier detection in euthymic older adults with marked cognitive complaints (CC) but normal neuropsychological test performance (Saykin 2006, Wang 2012). This study was aimed to evaluate connectome patterns in CC, mild cognitive impairment (MCI) or healthy controls (HC) based on diffusion tensor imaging (DTI). **Methods:** DTI was conducted in 69 participants (19 HC, 22 CC and 28 MCI) at 3T (Siemens Trio) using the following protocol: 48 non-collinear diffusion directions with b=1000 s/mm 2, echo time/repetition time=77/8300ms; 68 slices, 2x2x2 voxel size; plus 8 images with b=0s/mm 2. T1-weighted MPRAGE was acquired using the ADNI protocol. Anatomical images for each subject were segmented into different cortical regions using FreeSurfer 5.1, then parcellated into 463 regions of interest (ROIs) using the Connectome Mapping Toolkit (Cammoun 2012). Whole brain white matter (WM) fiber tracking was generated using the Diffusion Toolkit (Wang 2007). Weighted WM networks were constructed with fiber tracking between each corresponding pair of ROIs (Cheng 2012). Graph theory analysis was applied to compute connectome indices based on network metrics using the BCT package (Rubinov 2010). **Results:** Using age and sex as covariates, significant differences were found for the values of degree, strength and nodal efficiency ($HC > CC > MCI$, $p<0.05$), as well as shortest path length ($HC < CC < MCI$, $p<0.05$) in precuneus, orbitofrontal and middle frontal regions. Moreover, the CC group demonstrated significantly higher nodal efficiency than the HC and MCI groups in the parahippocampal region. **Conclusions:** Early structural network degeneration was revealed with graph theoretic methods in participants at-risk for AD. The findings are largely consistent with previous reports of the connectome in AD (Lo 2010) or individuals at-risk for AD (Brown 2011). Our results suggest alterations in the specific sub-networks may indicate interconnection changes for local brain regions in prodromal AD. Regionally increased parahippocampal nodal efficiency may imply a compensatory mechanism.

IC-P-119 COMPARISON OF CORTICAL THICKNESS BETWEEN KOREANS AND WESTERN INDIVIDUALS WITH MILD COGNITIVE IMPAIRMENT

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