3D mapping of associations between Amyloid-PET and CSF biomarkers and hippocampal morphology

John P. Andrawis [1], Kristy S. Hwang[2], Amity E. Green[2], Sona Babakchanian[2], Jonathan H. Morra[2], Jeffrey L. Cummings[2], Arthur W. Toga[2], John Trojanowski[3], Lesley Shaw[3], Clifford R. Jack[4], Michael W.Weiner[5], Paul M. Thompson[2], Liana G. Apostolova[2]
[1]University of Chicago, Chicago, IL, United States; [2]University of California Los Angeles, Los Angeles, CA, United States
[3] University of Pennsylvania, Philadelphia, PA; [4] Mayo Clinic, Rochester, MN, United States
[5] University of California San Francisco and VAMC, San Francisco, CA, United States

Background: Amyloid beta (Abeta), the primary aberrant protein that accumulates in the brains of Alzheimer's disease (AD) patients, can be measured in cerebrospinal fluid (CSF). Pittsburgh Compound B (PIB), a positron emission tomography (PET) ligand that readily binds to amyloid, allows for *in vivo* imaging of amyloid deposits in AD subjects. Here we explore in 3D the relationship between (1) hippocampal atrophy, the most established structural imaging biomarker in AD, and (2) CSF Abeta levels and parietal, precuneal and average cortical PIB standardized uptake value ratios (PIB SUVR).

Methods: We used an automated machine learning algorithm (AdaBoost), to segment the hippocampi in baseline 3D T1-weighted brain MRI scans of 282 ADNI subjects (83 cognitively normal (NC), 140 mild cognitive impairment (MCI) and 59 AD) all of whom had baseline CSF Abeta measurements, as well as the 1-year follow-up hippocampi of the subset of subjects who underwent PIB PET imaging at their 12-month follow-up visit (N=51; 12 NC, 31 MCI, 8 AD).

We then applied the hippocampal radial distance approach where we first develop 3D parametric surface mesh models of the hippocampi, then derive the medial core (centroid) for each hippocampal structure and then compute the radial distance from the medial core to each surface point (in mm) which we use for statistical comparisons.

CSF Abeta levels were extracted with the Multiplex xMAP Luminex platform and Innogenetics immunoassay kit-based reagent with monoclonal Ab4D7A3 Ab for Abeta.

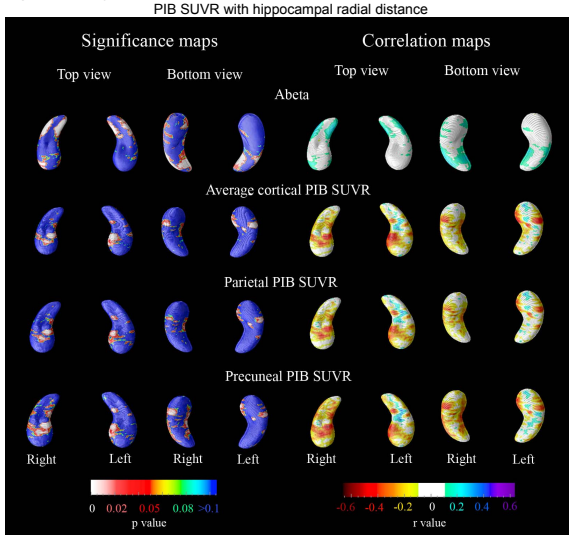
We used the individual mean precuneal, parietal and global cortical PIB SUVR measures from University of Pittsburg as provided on the ADNI website (http://www.loni.ucla.edu/ADNI/). The PIB SUVR was normalized to the cerebellum.

We ran linear regression analyses with hippocampal radial distance as the dependent variable using the CSF and PIB biomarkers as predictor variables. The 3D statistical maps were corrected for multiple comparisons by using 10,000 permutations with the threshold of p<0.01. Cumulative distribution function (CDF) plots – an intermediate step in false discovery rate (FDR) analyses, were used to rank the strength of the associations between CSF biomarkers and hippocampal radial distance.

Table 1. Demographic and biomarker data [mean (SD)]

CSF Biomarker Sample					
Variable (baseline)	**NC N=83**	**MCI N=140**	**AD N=59**	**All subjects**	**One-Way ANOVA, p-value**
Age, years	75.6 (5.2)	74.0 (7.3)	75.7 (7.9)	74.8 (6.9)	0.2
Education, years	15.6 (2.9)	16.0 (3.0)	15.3 (3.2)	15.7 (3.0)	0.4
MMSE	29.1 (1.0)	26.9 (3.3)	23.4 (1.8)	26.8 (2.6)	**<0.0001**
Abeta CSF level, pg/ml	209 (54)	160 (55)	142 (40)	171 (58)	**<0.0001**
PIB PET Subsample					
Variable (12 month)	**NC N=12**	**MCI N=31**	**AD N=8**	**All subjects**	**One-Way ANOVA, p-value**
Age, years	75.5 (6.7)	75.0 (8.4)	76.4 (6.6)	75.3 (7.7)	0.9
Education, years	15.2 (2.7)	16.5 (3.0)	14.6 (3.1)	15.9 (3.0)	0.2
MMSE	29.1 (0.8)	27.5 (2.0)	22.8 (3.5)	27.1 (2.9)	**<0.0001**
Parietal PIB SUVR	1.43 (0.3)	1.86 (0.4)	1.93 (0.3)	1.87 (0.5)	**0.001**
Precuneal PIB SUVR	1.48 (0.3)	1.94 (0.5)	2.16 (0.5)	1.44 (0.2)	**0.003**
Average cortical PIB SUVR	1.4 (0.2)	1.68 (0.3)	1.93 (0.3)	1.6 (0.3)	**0.005**

Figure 1. 3D significance and correlation maps of the association between CSF Abeta and PIB SUVR with hippocampal radial distance



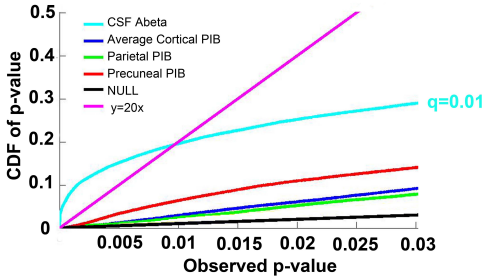
Results: Demographic and biomarker data are provided in **Table 1**.

CSF Abeta showed significant association with baseline hippocampal radial distance in the full sample (left $p_{corrected}$ = 0.003; right $p_{corrected}$ =0.0003; **Figure 1** top row). The CSF Abeta correlation maps showed the expected strong positive correlations (range r=0.2-0.5) with hippocampal radial distance in AD.

Precuneal PIB SUVR showed significant negative association with the right but not left hippocampal radial distance (right $p_{corrected}$ =0.016; **Figure 1** bottom row). Average cortical and parietal PIB SUVR failed to show significant associations with hippocampal atrophy.

The CDF plot (**Figure 2**) revealed that after map-wise FDR correction only CSF Abeta levels demonstrate significant correlation with hippocampal radial distance (i.e., the Abeta line is the only line crossing the y=20x line; q value=0.01).

Figure 2. CDF plot showing the direct comparison of the strength of the associations of Abeta and PIB SUVR with hippocampal radial distance



Conclusions: Although both CSF Abeta and PIB measure amyloid, CSF Abeta measures the soluble monomer, while PIB labels fibrilar amyloid. Although CSF Abeta, global and precuneal PIB SUVR showed significant associations with hippocampal radial distance on the 3D hippocampal maps, only CSF Abeta demonstrated an FDR-corrected significant association. Hippocampal atrophy seems to correlate better with CSF levels of monomer Abeta as opposed to PIB-labeled fibrilar Abeta in neuritic plaques.

This study was generously supported by NIA K23 AG026803 (jointly sponsored by NIA, AFAR, The John A. Hartford Foundation, the Atlantic Philanthropies, the Starr Foundation and an anonymous donor), the Easton Consortium for Alzheimer's Drug Discovery and Biomarkers, the Turken foundation, NIA P50 AG16570, NIBIB EB00856, NIBIB EB008281, NIBIB EB007813, NICHD HD 050735, NCRR P41 RR013642. Data collection was funded by NIA U01AG024904.