Concordance between CSF $A\beta_{1-42}$ (<550 pg/mL) and [^{18}F]flutemetamol was 57% and 53%, using visual and quantitative approaches, respectively. Among discordant cases, most showed isolated [^{18}F] flutemetamol positivity (75% using visual, 77% using quantification). **Conclusions:** While further analyses are ongoing for the remaining 74 patients, preliminary findings highlight the added value of [^{18}F]flutemetamol over standard diagnostic work-up. Discordance between CSF $A\beta_{1-42}$ and [^{18}F]flutemetamol PET highlights the issue of biomarker interchangeability in clinical settings.

IC-P-017 VOXEL-WISE DETERMINATION OF SENSITIVITY, SPECIFICITY, AND THRESHOLDS FOR AMYLOID POSITIVITY USING [^{18}F]FLORBETAPIR PET

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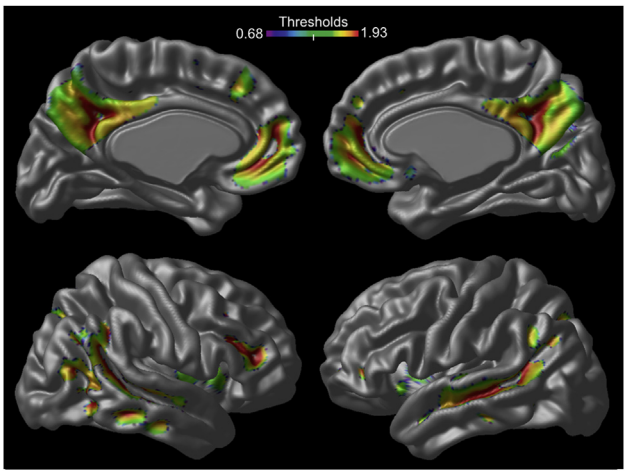
Background: Brain amyloid-β deposition is the core pathological feature of Alzheimer's disease (AD) and can be detected *in vivo* using positron emission tomography (PET). However, the importance of the regional patterns of amyloid-β abnormality has been highly questioned due to its widespread deposition over the cortex. Here, using a novel analytical framework free of conceptual assumptions, we assess the regional patterns of amyloid-β deposition that are associated with AD dementia. **Methods:** We assessed 211 control, 311 mild cognitive impairment, and 79 AD individuals who underwent [^{18}F]florbetapir PET at baseline as well as clinical assessments at baseline and at 2 years. Receiver operating characteristic curves, contrasting controls with AD individuals, assessed the least distance from point to the curve at every brain voxel, which provided the amyloid-β values with the best trade-off between sensitivity and specificity for AD. Finally, we generated a voxel-wise parametric map only with brain regions showing both sensitivity and specificity higher than 0.85. **Results:** Remarkably, the regions with the highest sensitivity and specificity for AD dementia were confined to the brain's default mode network in the precuneus, posterior cingulate, medial prefrontal, and lateral temporal cortices (Fig.1). In contrast, other brain regions with high amyloid-β burden such as the anterior cingulate had low sensitivity and specificity values. **Conclusions:** These results highlight that although amyloid-β deposition occurs widespread over the cortex, the deposition more strongly associated with dementia are confined to the brain's regions default mode network. Interestingly, our results showed



dissociation between the regional levels of amyloid-β burden and the sensitivity and specificity of this burden for a diagnosis of AD. This suggests that the selective regional vulnerability to the toxic effects of Aβ aggregates, at least, plays a role in the progression of AD.

IC-P-018 NEUROIMAGING-DEFINED AMYLOID AND CEREBROVASCULAR PATHOLOGY ARE ASSOCIATED WITH A NEUROMETABOLIC SIGNATURE OF ALZHEIMER'S DISEASE

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Background: To investigate whether white matter hyperintensities (WMH), an MRI-correlate of small-vessel cerebrovascular disease, are associated with a neurometabolic signature of Alzheimer's disease (AD), defined as the metabolic correlates of preclinical ß-amyloid (Aß) pathology and the apolipoprotein-E ε4 allele (APOE-ε4), the major genetic risk factor for sporadic AD. **Methods:** Cognitively normal participants (n=30, age=70±5.6 years, MMSE=29.2±1) received 11C-PiB-PET to quantify Aß, 7 Tesla fluid-attenuated inversion recovery MRI to quantitate WMH, and 7 Tesla high-resolution MR spectroscopic imaging to estimate N-acetylaspartate (NAA), myo-inositol (mI), total-choline (tCho), and creatine (Cr) in posterior cingulate and precuneus (PCP) gray and white matter. We examined relationships of Aß, WMH, and APOE-ε4, and their interactions, with brain metabolites. **Results:** Higher levels of Aß (r= -0.64, p<0.001) and higher WMH volume (r= -0.45, p=0.02) were associated with lower NAA/mI in gray matter. Participants with both high Aß and high WMH had lower NAA/mI compared to those with none or with high level of either Aß or WMH (significant Aß x WMH

interaction; F=5.38, p=0.03). APOE-ε4 carriers had lower NAA/mI compared to non-carriers (t=2.24, p=0.03). tCho/Cr in white matter was associated with Aß (r= -0.53 p=0.004) and WMH (r= -0.51; p=0.006); APOE-ε4 carriers with high WMH showed strongest reductions of tCho/Cr (significant APOE-ε4 x WMH interaction, F=6.45, p=0.02). **Conclusions:** These findings suggest that a neurometabolic signature of AD, defined by metabolic correlates of Aß and APOE-ε4 in older adults, consists of reduced NAA/mI in gray matter and reduced tCho/Cr in white matter. We speculate that these metabolic differences reflect neuronal impairment, glial activation, and altered choline metabolism. This neurometabolic signature of AD is also associated with WMH, both independently and synergistically with Aß and APOE-ε4, emphasizing the importance of small-vessel cerebrovascular disease for AD pathogenesis.

IC-P-019 EFFECTS OF USING A NOVEL LONGITUDINAL PROCESSING PIPELINE FOR MEASURING CHANGE OVER TIME IN PIB-PET

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Background: Accurate and reliable automated measures of change-over-time in amyloid PET are crucial to observational and clinical trials for Alzheimer's disease. Previous works have examined how varying methodological choices, such as reference region, affect change measurements computed from cross-sectional (computed intra-timepoint) measurements. This work examines the effects of using longitudinal (simultaneous cross-timepoint) measurement methods. **Methods:** We implemented a novel, automated longitudinal pipeline. Corresponding serial T1-weighted images were coregistered using a group-wise ANTs nonlinear registration to produce a mean-space T1-weighted single-subject template image (T1-SST). This T1-SST was segmented with SPM12. ANTs nonlinear registration to an in-house standard atlas was used to localize regions on T1-SST (a standard cortical target and seven candidate reference regions) for SUVR calculations. Serial PiB scans were coregistered using group-wise rigid registration with SPM12 to produce a mean-space PiB single-subject template image (PET-SST). A rigid registration between the PET-SST and the T1-SST was used to

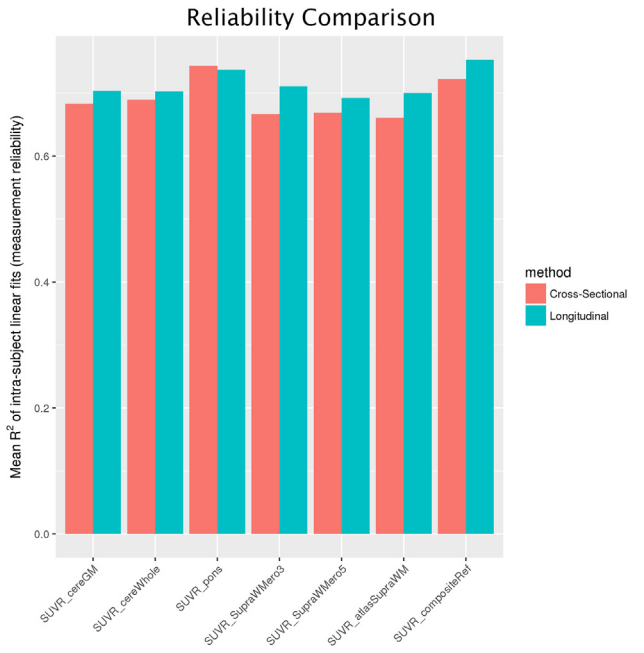

Figure 1. The reliability of intra-subject trajectories using the proposed longitudinal method was > that of the traditional cross-sectional method in 6/7 comparisons with varying reference regions.

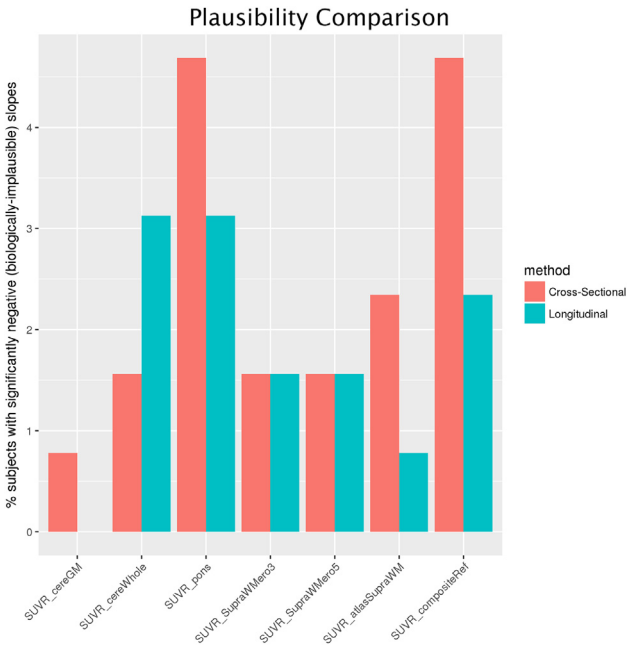

Figure 2. The percentage of subjects with biologically-implausible, significantly decreasing slopes using the proposed longitudinal method was ≤ that of the traditional method when using 6/7 tested reference regions.

Table 1
Reliability and plausibility performance for each combination of method and reference region

Method	Reference Region	Mean R^2 (reliability)	% Significantly Negative (implausible) slopes
Cross-Sectional	SUVR_cereGM	0.684	0.781
Longitudinal	SUVR_cereGM	0.704	**0.000**
Cross-Sectional	SUVR_cereWhole	0.690	1.563
Longitudinal	SUVR_cereWhole	0.703	3.125
Cross-Sectional	SUVR_pons	0.744	4.688
Longitudinal	SUVR_pons	0.737	3.125
Cross-Sectional	SUVR_SupraWMero3	0.667	1.563
Longitudinal	SUVR_SupraWMero3	0.711	1.563
Cross-Sectional	SUVR_SupraWMero5	0.669	1.563
Longitudinal	SUVR_SupraWMero5	0.692	1.563
Cross-Sectional	SUVR_atlasSupraWM	0.661	2.344
Longitudinal	SUVR_atlasSupraWM	0.700	0.781
Cross-Sectional	SUVR_compositeRef	0.723	4.688
Longitudinal	SUVR_compositeRef	**0.753**	2.344