value ratio (SUVRs) ≥1.1, measured from a standard space template consisting of 6 cortical regions. For comparison to a whole-cerebellar reference region, a second normalization was performed on the longitudinal data using a centrum semiovale region as a correction factor (Figure). This method has been shown to improve signal to noise, while preserving the ability to use cerebellar SUVRs at baseline[1]. Analysis-of-Covariance models adjusted by baseline, study, treatment and age were used to assess baseline-to-endpoint change between treatment and placebo groups. For sample size estimations, 80% power and α=0.05 were used to detect magnitude of observed 18 month changes from baseline in the placebo group. **Results:** Using a whole-cerebellar reference region at baseline and endpoint, least squares mean SUVRs for the placebo group increased 0.004±0.0129 (0.49%±0.91), and for the active treatment group decreased 0.006±0.0137 (0.19%±0.96)(p=0.62). Power analysis revealed a sample size of n=4056 to detect a difference between 18 month placebo group change and baseline SUVRs (i.e. no change in treatment group from baseline). White matter adjustments resulted in a mean increase of 0.011±0.0075 (0.79%±0.54) in the placebo group and mean decrease of 0.008±0.008 (-0.6%±0.57) in the active treatment group (p=0.08); the calculated sample size fell to n=421. **Conclusions:** Adjusting longitudinal SUVRs with a white matter reference region in these phase 3 anti-amyloid treatment trials increased mean change detection and decreased variance. This method resulted in a substantial improvement in statistical power to detect change. Reference: Abhinay Joshi, Michael Pontecorvo, Michael A. Navitsky, Ian A. Kennedy, Mark Mintun, Michael D. Devous. Measuring change in beta–amylod burden over time using florbetapir-PET and a subcortical white matter reference region. Alzheimer's Dement. 2014;10(4):902.

$$Visit\ 1 = \frac{\frac{Cortex\ V1}{Cereb\ V1}}{\frac{WM\ V1}{WM\ V1}} = \frac{Cortex\ V1}{Cereb\ V1} \qquad Visit\ 2 = \frac{\frac{Cortex\ V2}{Cereb\ V2}}{\frac{WM\ V2}{\frac{Cereb\ V2}{WMV1}}} = \frac{Cortex\ V2 * WM\ V1}{Cereb\ V1 * WM\ V2}$$

Figure. Secondary normalization for white matter reference region
Figure: White matter normalization – the original baseline (Visit 1) cerebellar SUVR is used, but a new endpoint (Visit 2) accounts for the baseline to endpoint change observed in the WM.
WM = White Matter; Vl = Visit 1; V2 = Visit 2; Cereb = whole cerebellum

IC-P-031 MEDIAL TEMPORAL LOBE CHANGES WITH ENDOVASCULAR PROCEDURES

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Background: Vascular disease contributes powerfully to the trajectory of decline in AD and also to vascular dementia. Whereas the medial temporal lobes (MTL) are vulnerable to AD, this region is not typically a focus of study in vascular dementia. For patients with severely occluded carotid arteries, carotid endovascular procedures (carotid endartorectomy or stenting) are important interventions which rapidly restore flow to the brain and prevent stroke. Our lab has found that several patients undergoing these procedures experience memory declines. Because the MTL is crucial for memory we investigated whether there were volumetric changes in this region following endovascular procedures. **Methods:** Structural MRI (T1) images were collected in 42 patients before and after endovascular procedures. Postoperative MRI was collected within 48 hours after intervention. Automated volumetric measurement was performed using Freesurfer. The volumes were normalized (divided by the total intracranial volume) and difference scores comparing pre to post surgery were computed for each patient. These change scores were compared to zero using t-tests for each MTL. **Results:** T-tests comparing volumetric surgical change scores for left and right MTL indicated that there was an increase in volume from pre to post procedures bilaterally (p<.01). The effect was observed in most patients (31 in left MTL and 30 in the right MTL) irrespective of the side of the procedure. **Conclusions:** This is the first study to report an increase in MTL size associated with carotid endovascular procedures. The functional significance on cognition is unclear but the fact that procedures to treat occluded flow alter MTL volume suggests that vascular occlusive disease has direct effects on the MTL.

IC-P-032 QUANTIFYING NEOCORTICAL STRUCTURAL CHANGES FOR CLINICAL TRIALS IN ALZHEIMER'S DISEASE: COMPARISON BETWEEN TENSOR-BASED MORPHOMETRY AND LONGITUDINAL FREESURFER

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Background: Accurate and reliable quantification of structural brain changes, within a regulatory compliant framework, is important in clinical trials for Alzheimer's disease (AD). Cortical changes relevant to AD pathology have been reported in various regions including isthmus cingulate, precuneus, inferior parietal, temporal pole and prefrontal cortex[1,2]. We report the performance of atrophy measurements for these structures using tensor-based morphometry (TBM)[3], and compare to changes in cortical thickness measured with longitudinal FreeSurfer (LFS_Th)[4] on the standardized ADNI dataset[5]. **Methods:** 3DT1 MRI sequences from ADNI-1/2 were analyzed using pair-wise approaches to assess changes in volume (TBM) and cortical thickness (LFS_Th). Thickness changes over volume from the LFS processing suite was chosen for comparison due to lower variability (data not presented). Baseline and Month-3 data from 20 ADNI-2 normal controls

Table 1
Generalized AUCs for each cortical region and method at M12 and M24

	TBM Month-12	LFS Th Month-12	TBM Month-24	LFS Th Month-24
Temporal pole	0.72	0.64	0.76	0.69
Isthmus cingulate	0.69	0.61	0.74	0.63
Precuneus	0.67	0.61	0.68	0.61
Interior parietal	0.64	0.61	0.66	0.63
Prefrontal	0.62	0.56	0.68	0.65

Note: Generalized AUCs were calculated by computing probability that two random subjects are properly ranked with respect to ordinal outcome with two or more levels.

Table 2
DeLong test results (AUC-TBM/AUC-LFS_Th (P value)) in comparing groups at M12 and M24

	AD/NC Month-12	AD/NC Month-24	AD/LMCI-c Month-12	AD/LMCIc Month-24	LMCI-c/LMCI-nc Month-12	LMCI-c/LMCI-nc Month-24
Temporal pole	0.84/0.76 (0.013)	0.92/0.82 (0.002)	ns	ns	0.73/0.57 (<0.001)	0.73/0.64 (0.014)
Isthmus cingulate	0.81/0.67 (0.001)	0.88/0.72 (< 0.001)	0.59/0.51 (0.041)	ns	ns	0.72/0.60 (0.002)
Precuneus	0.77/0.68 (0.007)	0.82/0.70 (< 0.001)	ns	ns	ns	0.69/0.61 (0.010)
Interior parietal	0.73/0.67 (0.054)	0.79/0.73 (0.060)	ns	ns	ns	ns
Prefrontal	0.70/0.60 (0.001)	0.82/0.77 (0.065)	0.57/0.54 (0.041)	ns	ns	ns

Note: ns (Not Significant), LMCI-c (Late MCI-converter), LMCI-nc (Late MCI-non-converter).

(NCs) were used for test-retest purposes. Absolute symmetrized percent change (ASPC)[6] was calculated to assess variability. Baseline, Month-12 and Month-24 ADNI-1 data were used to quantify percent changes for 493 subjects (99 ADs, 115 LMCI-converters, 115 LMCI-non-converters and 164 NCs). Generalized areas under curve (AUCs) were calculated and the DeLong test[7] was performed to compare receiver operating characteristic (ROC) curves between methods. Linear regression was performed to test bias. **Results:** Mean ASPC (%) between Baseline_-Month-3 scans from NCs were smaller for TBM than LFS_Th for all regions, indicating lower variability with the TBM method (33% for inferior parietal up to 56% fortemporal pole). Generalized AUCs and ROC results for Month-12 and Month-24 changes are reported in Tables 1 and 2. The TBM method yielded systematically larger AUCs and better ROC discrimination between several category pairs. Linear regression of Month-12 and Month-24 changes yielded intercepts close to zero for all regions and subgroups, indicating negligible bias for either TBM or LFS_Th methods. **Conclusions:** The TBM method successfully and reliably quantified changes over time for various cortical regions, and showed improved sensitivity to differentiate subgroups compared to LFS_Th. A pair-wise analysis approach to quantify changes using TBM may be a useful option for clinical trial applications, considering the intrinsic limitation of LFS_Th which needs to be run after scans from all required visits are acquired.
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IC-P-033 TREATMENT WITH 17β-ESTRADIOL IN POSTMENOPAUSAL WOMEN IS ASSOCIATED WITH LOWER PIB-PET RETENTION

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Background: Treatments to reduce the amyloid plaque burden in the aging, cognitively normal population may prevent or delay the development of dementia. Pittsburgh compound B (PiB) binds to amyloid plaque and provides a surrogate for amyloid β pathology using PET. PiB-PET retention is a frequent finding in the aging, cognitively normal population. We investigated whether the treatment of postmenopausal women with menopausal hormone therapy (MHT) would have an association with amyloid burden measured by PiB-PET. **Methods:** Participants were recruited from the Kronos Early Estrogen Prevention Study (KEEPS), which was a randomized, placebo controlled trial to evaluate cardiovascular effects of MHT in recently menopausal women. PiB imaging was performed on a subgroup of subjects about 7 years after initiating 4 years of MHT where women within 6-36 months of their last menses had been randomized to either oral conjugated equine estrogen (CEE), Premarin, 0.45mg/day (N=17); or transdermal 17β-estradiol (TE), Climara, 50µg/day (N=21) (each with progesterone 200mg/day for 12 days/month) or placebo pills and patch (N=30). Participants had full clinical and neuropsychometric assessments. PiB images from each group were compared after treatment using a global SUVr measurement as a continuous measure. **Results:** Positive PiB-PET scans were seen in 3(18%), 1(5%) and 1(3%) with median(range) SUVr's of 1.27 (1.19, 1.76), 1.25 (1.12, 1.75), 1.28 (1.20, 1.44) in the CEE, TE, and placebo groups respectively. A trend for reduced PiB retention was seen in the TE group vs. placebo (p=0.08). Among women who were APOE 4+ (N=18), we observed differences in PiB retention between CEE vs. TE (p=0.049) and TE vs. placebo (p=0.055) groups. No significant differences were observed in APOE 4- participants (n=40). (Figure). **Conclusions:** These preliminary findings in a small number of women suggest an active role of TE for reducing amyloid brain deposition in postmenopausal women when treated for 4 years, shortly after menopause. These data may provide the rationale for a clinical trial to further investigate these findings in a larger population. These findings would support the observation that 17β-estradiol reduces the release of Aβ peptides in preclinical models. This interaction seems to be most pronounced in APOE 4+ women.

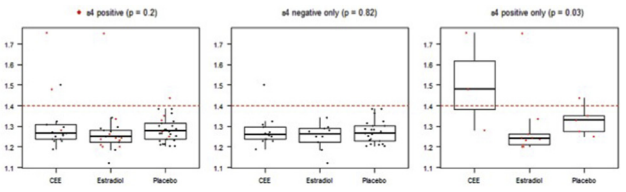

Figure. Boxplots of PiB ratios by treatment status. For ε4 positive only (right box), the p-values between 3 groups are as follows; CEE vs. Estradiol = 0.049, CEE vs. Placebo = 0.25 and Estradiol vs. Placebo = 0.055. The box on left has all subjects with e4 positives in red. The middle box has e4 negative subjects only. P-values are from Kruskal-Wallis and Wilcoxon rank sum tests. PiB cutoff for positivity at 1.4 is shown by a red-hashed line.