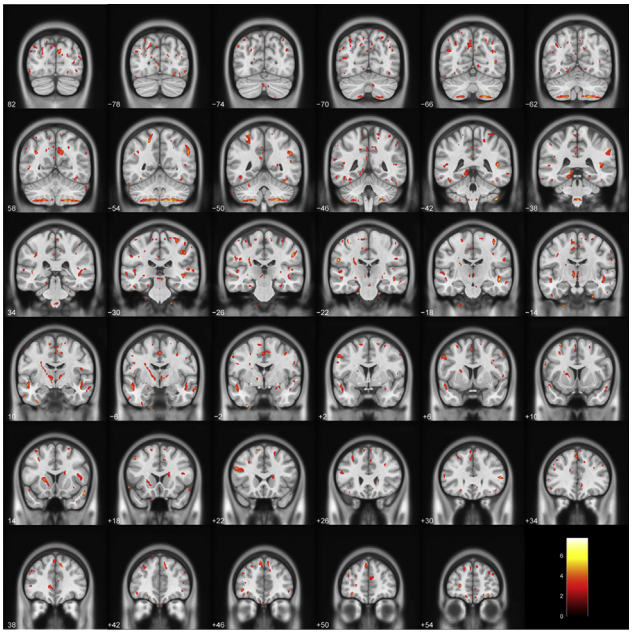

patients. Considering that R2 relaxation rate is a factor of iron content and tissue structure, this pattern could be indicative of white matter alterations in Alzheimer's disease. This hypothesis is congruent with data showing that AD has an integral white matter component.

IC-P-029 MAGNETIC RESONANCE IMAGING OF APP/PS1/TAU MICE ON GRADATED IRON DIETS

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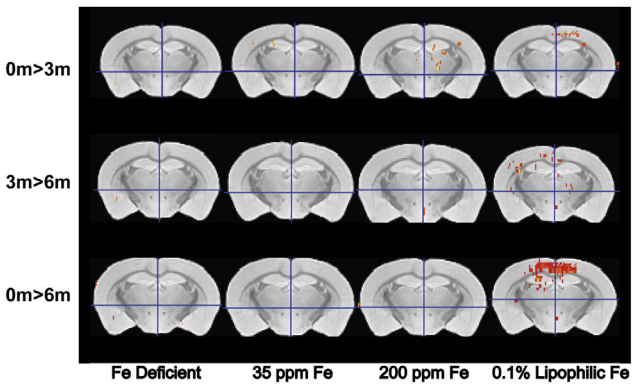
Background: There is converging evidence that iron overload is involved in both amyloid-beta (Aβ) plaque and neurofibrillary tangle (NFT) formation. Our previous results have demonstrated that hypo-intensities on T_2- and T_2*-weighted MRI datasets coincide with Aβ plaques in AD and transgenic neural tissue. There are crucial unanswered questions in the current literature on how iron and amyloid fibrils are involved in plaque and tangle genesis in the living brain and the neurotoxic impact of amyloidogenesis. We hypothesize that iron is a cofactor in the genesis of Aβ plaques and plays a synergistic function in relation to Aβ plaque neurotoxicity. The goal of this research is to 1) determine the *in vivo* relationship between iron and AD pathology, 2) observe the effects of different iron diets on spatial and learning memory using escape maze tasks, and 3) establish the cyto-architectural basis of AD pathology in relation to MR metrics. **Methods:** Four groups of six APP/PS1/Tau transgenic mice were randomized into four diet groups consisting of Fe deficient, 35 mg/kg Fe, 200 mg/kg Fe, and 0.1% lipophilic iron. Mice were scanned on a 7.0 T system at baseline and at three month increments for one year along with cognitive and blood biomarker measures. Group based parametric map analysis and region of interest (ROI) based transverse relaxation metrics were generated. **Results:** Group based transverse parameter maps and ROI analysis of mice fed the iron diets demonstrate that mice have shorter transverse relaxation in a gradated step-wise fashion with increasing iron diet in the same cortical regions. **Conclusions:** The parametric group analysis and segmentation changes confirm that high iron diets significantly alter the APP/PS1/Tau brain. Our previous data has shown that transverse relaxation is a measure of plaque formation and iron loading; as such, the cortical relaxation changes are hypothesized to reflect an accumulation of iron and Aβ plaques genesis in the cortex. This research will generate new information for understanding the role of homeostatic iron overload in Aβ plaque and NFT formation within the AD brain to determine how iron levels affect plaque morphology, pTau formation, iron management, inflammatory response, and cognition.



IC-P-030 COMPARISON OF REFERENCE REGIONS FOR IMPROVED DETECTION OF CHANGE IN FLORBETAPIR PET FROM PHASE 3 SOLANEZUMAB TRIALS

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Background: Amyloid-PET is commonly utilized in Alzheimer's disease(AD) anti-amyloid therapy trials for eligibility requirements and longitudinal evidence of target engagement. Improving methodologies to detect longitudinal change in amyloid-PET is of particular importance. Although cerebellum is a widely utilized reference region for cross-sectional quantitative evaluations, it may not be optimal for longitudinal assessments. We compared use of atlas based cortical white matter and whole-cerebellum reference regions for accuracy and power for detecting longitudinal change in Phase 3 solanezumab trial data. **Methods:** Florbetapir-PET scans were analyzed from 140 participants (72 placebo, 68 solanezumab) with mild dementia due to AD from the 18-month, randomized, placebo-controlled EXPEDITION 1&2 solanezumab studies. Participants had florbetapir positive scans at baseline, determined by mean cortical-to-whole-cerebellar standard uptake

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.