

of the hippocampus showed association between [¹⁸F]FDG declines and structural shrinkage. The left motor cortex and thalamic nuclei as well as the right primary somatosensory cortex showed dissociation between structural changes (expansion) and [¹⁸F]FDG declines. **Conclusions:** McGill-R-Thy1-APP allows for longitudinal biomarker measures without confounding effects of neurofibrillary tangles or cell death. In fact, the present results suggest that brain abnormal amyloid aggregates present in the McGill-R-Thy1-APP rat leads to expansion or shrinkage of grey matter structures and progressive hypometabolism. However these processes occur in synchrony in specific brain regions. These suggest a complex interface between amyloid pathology and pathophysiological mechanisms involved in structural declines in transgenic animals.

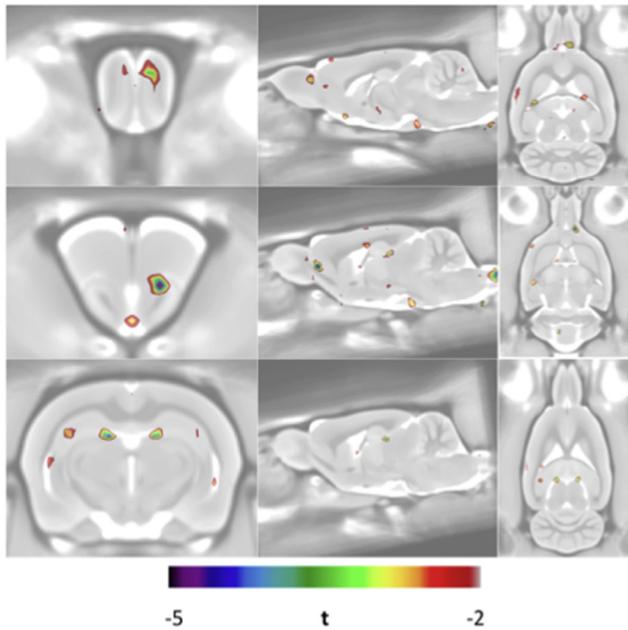


Figure 1. t-stat map of regions that shrink when the metabolism decreases throughout the brain.

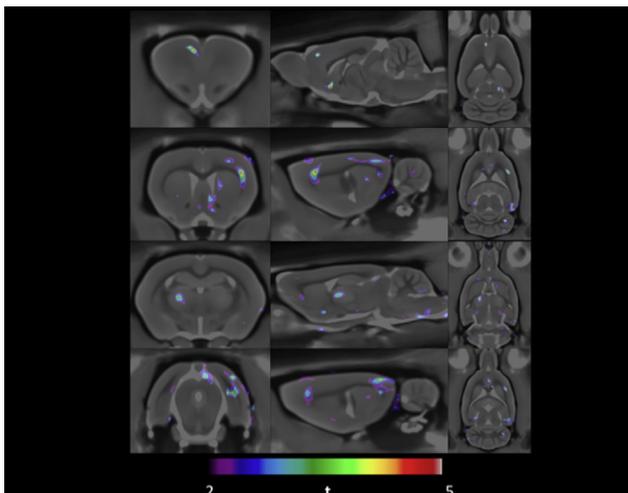
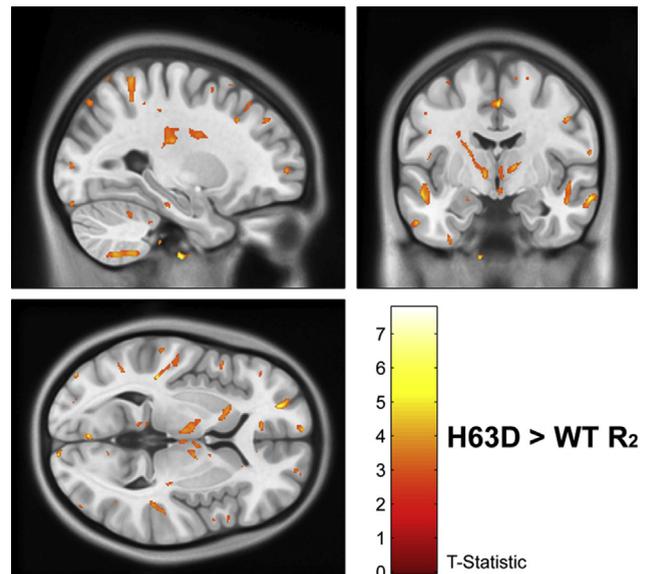


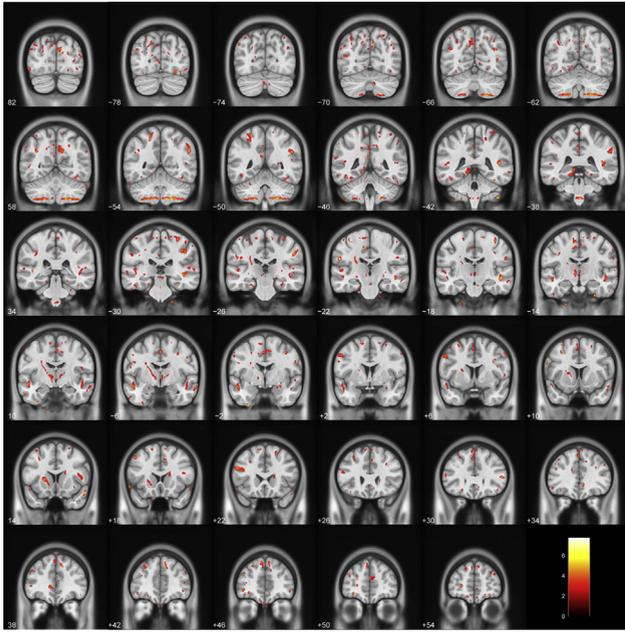
Figure 2. t-stat map of regions that expand when the metabolism decreases throughout the brain.

IC-P-028 DIFFERENTIAL MRI RELAXATION IN ALZHEIMER'S PATIENTS WITH MUTANT HFE AND TRANSFERRIN GENOTYPES

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Background: Iron accumulation in the brain and oxidative stress are observed in a number of neurodegenerative disorders such as Alzheimer's disease (AD). Common mutations that lead to high iron overload has been associated with two gene variants within the HFE gene, C282Y and H63D, and within the transferrin (Tf) gene, C2. Within Alzheimer's disease these mutations are found with increased frequency in patients (estimates are between 20-50%). The goal of this work was to understand how HFE and C2 mutations effect transverse relaxation in the AD brain with the hypothesis that these mutations will result in increased transverse relaxation rate within the brains of AD C282Y, H63D, or C2 carriers. **Methods:** Thirty-eight mild Alzheimer's disease patients (13M, 25F) were enrolled. Of these, 7 subjects (1M, 6F) were heterozygous and 1 subject homozygous (1F) for the H63D mutation, 3 subjects (2M, 1F) were heterozygous C282Y mutation, and 4 subjects were heterozygous (2M, 2F) for the TFC2 mutation. All patients were scanned on a 3.0 T system and group based parametric map analysis was performed on the stratified patient populations: those with high iron mutations (IRON +; H63D, C282Y, or C2) and those with all wild-type genes (IRON -). **Results:** The group based R₂ parametric analysis demonstrates that AD patients with high iron mutations (IRON+) have increased R₂ rates specifically within white matter regions of interest. **Conclusions:** The stratification of AD patients based on IRON + genetics and determination that there are relaxation differences specifically in white matter is a highly novel finding. The cause for the white matter relaxation metrics are believed to be multi-faceted and not only related to the high iron status of AD IRON + carriers. As the relaxation rate alterations are found exclusively in white matter, we hypothesize that there are white matter modifications in AD IRON +





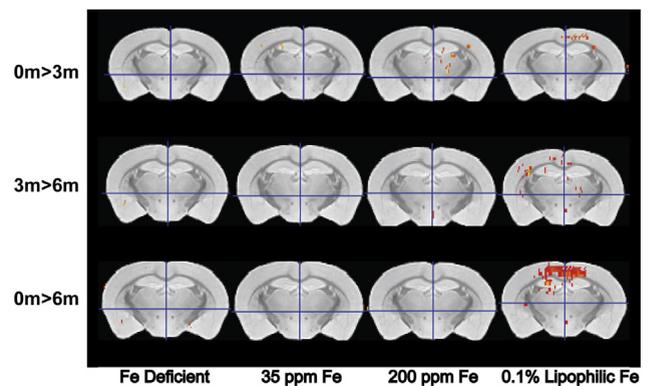
patients. Considering that R2 relaxation rate is a factor of iron content and tissue structure, this pattern could be indicative of white matter alterations in Alzheimer's disease. This hypothesis is congruent with data showing that AD has an integral white matter component.

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 ($A\beta$) 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 $A\beta$ 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 $A\beta$ plaques and plays a synergistic function in relation to $A\beta$ 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 graduated 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 $A\beta$ plaques genesis in the cortex. This research will generate new information for understanding the role of homeostatic iron overload in $A\beta$ 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