Differential MRI Relaxation in Alzheimer's Patients with Mutant HFE and Transferrin Genotypes

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Introduction: 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[1]. Within Alzheimer's disease these mutations are found with increased frequency in patients (estimates are between 20-50%). The HFE and C2 mutations results in a conformation change of its structure such that the HFE bound to the Tf receptor does not hinder the binding of Tf to the TfR, allowing Tf to freely bind permitting multiple iron molecules to pass into the cell. These mutations result in iron dyshomeostasis, increased oxidative stress, glutamate release, tau phosphorylation, and alteration in inflammatory response[2]. 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. An anatomical $3DT_1$-weighted and a multi-echo T_2-weighted spin-echo (9 echoes, 11 – 99 ms) protocol were obtained and parametric relaxation R_2 rate maps generated. All datasets were coregistered, resliced, realigned to a template brain, and segmented using SPM8. AD patients were stratified into two groups: those with high iron mutations (IRON +; H63D, C282Y, or C2) and those with all wild-type genes (IRON –). For parametric map analysis, the relaxation maps were normalized to the template brain and voxel based analysis was performed using a group based method (cluster size ≥ 10 and $p \leq 0.005$) in SPM8. To account for any potential confound in patient age and gender, these were used as covariates in the analysis.

Results: The group based R_2 parametric analysis demonstrates that AD patients with high iron mutations (IRON+) have increased R_2 rates specifically within white matter regions of interest (Figs. 1 and 2). A region of interest mask was not used in the analysis, yet all highlighted regions are found extensively throughout cortical and subcortical white matter regions. R_2 measures were not found to correlate to decreased cognitive score in the IRON+ AD patients, as IRON + and – patients did not differ in their cognitive measures.

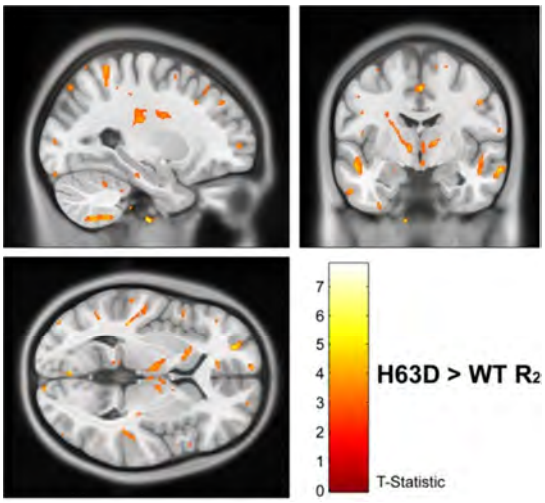

Figure 1: Close-up of group based parametric differences showing increased R_2 rates within AD IRON + > AD IRON – patients.

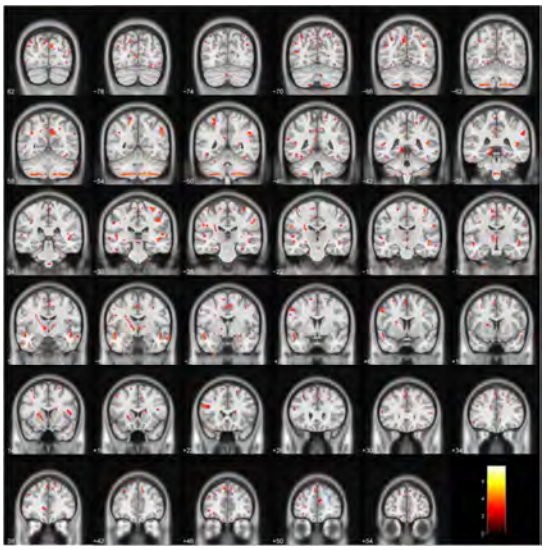

Figure 2: Group based mosaic parametric differences showing increased R_2 rates within AD IRON + > AD IRON – patients.

Discussion: Increased iron load has been proposed as a putative risk factor and potential causative factor in the development of Alzheimer's disease. MRI measures have shown differences in relaxation measures between AD patients and controls. 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 a white matter modifications in AD IRON + patients. Considering that R_2 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 theory is congruent with the hypothesis and data showing that AD has an integral white matter component[3,4]. Future longitudinal analysis on the relation of IRON + genetics and AD progression is planned as well as histological analysis of IRON + and – AD patient white matter to verify these findings on a macro-molecular level.

References: **1** – Feder *et al.* Nat Genet 1996, 13, 399-408, **2** – Nandar *et al.*, The Journal of nutrition 2011, 141, 729S-739S, **3** – Lu. *et al.*, JAD, 2014;39(2):261-269, **4** – Bartzokis *et al.*, Neurobiol Aging 2009;32(8):1341-1371.