^{1}H MR spectroscopy of the hippocampus in pre-clinical Alzheimer's Disease

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Introduction: Recently, amyloid ß (Aß) PET imaging along with assessments of cerebrospinal fluid (CSF) levels of Aß, tau and phosphorylated tau (p-tau), have revolutionized the field of early Alzheimer's disease (AD). Individuals who are positive for these Aß and tau biomarkers, but are cognitively normal, can be defined as "asymptomatic at risk for AD dementia." Many of them, however, do not progress to clinical AD. Further refinement of the staging criteria is therefore warranted, with one avenue being through brain proton MR spectroscopy (^{1}H MRS). In this study, cognitively normal individuals are divided into two categories based on their risk for developing AD, as determined by genetic screening and CSF levels of Aß and tau. We hypothesize that compared to those with low-risk, high-risk subjects will have lower glutamate+glutamine (Glx) levels in the hippocampus, and that the effect size of this difference will be larger than lower *n*-acetyl-aspartate (NAA) or higher *myo*-inositol (mI), the main findings in AD[1].

Methods: **Subjects** were characterized as "cognitively normal" through an extensive cognitive testing battery, a physical exam with MRI screening, as well as blood work-up for general medical conditions. The cohort received a lumbar puncture for CSF collection and genotyping for determining the presence of APOE ε4, a known risk for AD. "High-risk" individuals were defined as one or more of the following: (1) APOE ε4 carriers; (2) Aß1-42 < 442 pg/mL; (3) p-tau > 60 pg/mL. The "low-risk" group was composed of APOE ε4-negative individuals, with Aß1-42 and p-tau at the opposite sides of the cut-offs. **^{1}H MRS.** Subjects were scanned in Siemens Prisma 3T using 20-channel head coil. Volume of interest (VOI=3.38mL) was placed in the left hippocampus. Metabolites were measured with semi-LASER sequence with wide bandwidth GOIA[2] refocusing pulses. A long TE of 120ms was chosen for negligible contamination from macromolecules along with optimal detection of J-coupled metabolites: Glx and mI. Water suppressed spectra were acquired with 256 averages and TR=1.5s. Metabolites were quantified with LCModel[3] with basis set simulated in FID-A[4] and corrected for voxel CSF fraction.

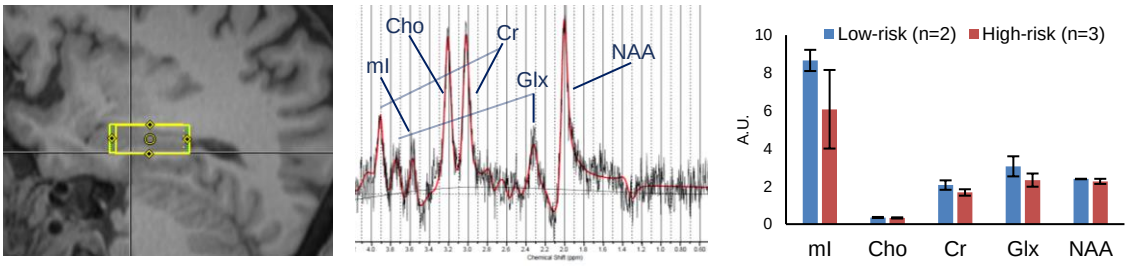

Figure 1. Left and central panels: VOI placement in the hippocampus and the corresponding fitted metabolite spectrum of a high-risk subject. **Right panel:** Preliminary assessment of brain metabolite levels in low-risk and high-risk groups (arbitrary units).

Results: Currently, 5 volunteers have been recruited (3 high-risk and 2 low-risk). All high-risk subjects were APOE ε4 carriers (one homozygous), with two distinct subjects also falling within the high-risk ranges in CSF Aß and p-tau. Illustrations of the ^{1}H MRS measurement and preliminary data from both groups are depicted in Fig.1. No statistical comparisons were done, since at this study stage the sample size is small and the groups are not age-matched.

Discussion: To our knowledge, only a few studies used ^{1}H MRS in cognitively-normal subjects at high-risk for AD[5,6]. The novel aspects here include the quantification of Glx, as a candidate marker for early pathology, and the investigation of the hippocampus, the hallmark target of AD. The semi-LASER sequence and long TE allowed for negligible chemical shift displacement artefact and simplified quantification. This recently-started study is on track to recruit 40 individuals. The sample size was determined so that the study would have >80% power to detect a 17% mean difference in concentrations between the two cohorts. Analyzed results (Fig.1) are encouraging, as they show metabolic coefficients of variation in line with those used to yield the above sample size (~16%).

Conclusion: Our MRS protocol enabled high precision measurement of the hippocampus in under 10 minutes, minimal macromolecular contamination, and detection of J-coupled metabolites, such as Glx and mI. Preliminary data suggests good reproducibility and possible changes in several metabolites which will be investigated as the study recruits more participants.

References: (1) Gao and Barker, AJNR 2015; (2) Andronesi et al. JMRI 2010; (3) Provencher S. MRM 1993; (4) Simpson et al. MRM 2017 (5) Voevodskaya et al. Neurology, 2016. (6) Godbolt et al. Neurology, 2006