PILOT LIPID MRI STUDY PROTOCOL AND STATISTICAL ANALYSIS

OFFICIAL TITLE: TRIGLYCERIDE EFFECTS ON BLOOD FLOW IN THE HUMAN BRAIN

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Rationale:

Overview: High fat feeding (HFF) is a risk factor for Alzheimer's disease (AD), but this risk factor is modulated by APOE genotype. Acute meal studies including lipid tolerance tests are increasingly being used to understand mechanisms by which diet affects disease processes. We have consistently shown that E4 carriers respond differently to HFF in acute meal challenges; we wish to further explore this phenomenon in older adults by assessing cerebral blood flow (CBF), given its tight coupling to brain metabolism. Here we propose to use arterial spin labeling (ASL) MRI as this non-invasive imaging technique can detect small changes in global and regional CBF, and acute ∆CBF in response to glucose, insulin and mixed meals have been demonstrated in humans. Project objectives: 1. To determine which time point (1, 2, or 3 hours) produces the most robust ∆CBF after ingestion of a lipid drink in 30 older adults. 2. To determine which regions of the brain respond to HFF. 3. To determine whether E4 status influences ∆CBF to lipid ingestion at the global or regional level.

Procedure:

Overview: Participants (n=30) will be recruited from Seattle-based registries. Participants will arrive at the South Lake Union UW translational research unit (TRU) in a fasting state and after giving informed consent they will undergo the first ASL MRI image acquisition. Then they will drink the lipid product (just under half a cup of heavy whipping cream) and undergo 3 more acquisition scans at 1, 2, and 3 hours post drink. They will then be offered lunch for purchase at the UW cafeteria and discharged home.

Participants: All study procedures will be submitted to the UW Institutional Review Board for approval before any participants are recruited; IRB application for this project has been started and will be submitted by October 22, 2019. We maintain a database from the Meal and Memory study which contains over 50 participants, several of whom know their APOE genotype. Inclusion criteria are age 55 and older, and able to read English, give informed consent, undergo MRI and ingest dairy products. For the study visit, participants will be asked to fast for 8 hours. They will undergo informed consent, and then the protocol will begin: First a 30 minute ASL protocol will be run, then the participant will be given the heavy cream to drink over 5 minuts (100 mls just under ½ cup; 370 calories, 40.4 grams of total fat, 23.6 grams of saturated fat). Participants will then undergo 3 more 15-minute scans at 1, 2, and 3 hours post drink. After the last MRI image acquisition, lunch will be offered, participants will receive a gift card, and be discharged.

MRI protocol: For the ASL protocol, we will use pseudo-continuous arterial spin labeling to measure CBF in ml/100g/min as a marker of perfusion for improved signal quality. In this approach, magnetically labeled arterial blood water serves as the endogenous contrast. Experiment: As per the consensus recommendations, we will use a sequence (5.5 minutes) with long label duration = 1.8 s, long post-labeling delay = 2 s, with labeling offset = 25-30 mm, slices = 20, spatial resolution = 3.5×3.5×5 mm3, field of view = 240×240×100 mm3, SENSE-factor = 2, TR/TE= 5000/18 ms. We will apply dual adiabatic background suppression pulses to minimize gray and white matter tissue contamination at TI = 2.05 and 3.25 s. Finally, we will acquire an equilibrium magnetization scan (M0, 1 minute), identical to the above scan, but with TR = 10,000 ms and no labeling or background suppression.

Analysis: Analysis will be done under the supervision of Dr. Rane and Dan Hippe with the UW Diagnostic Imaging Sciences Center (DISC). We will first apply motion correction to the arterial spin labeling images using FSL-MCFLIRT and register them to the M0 image. Then, we will perform a pair-wise subtraction between the control and null images and apply a two-compartment model to quantify CBF. We will co-register the resulting CBF map to the T1 scan followed by a transformation to MNI space. The temporal regions such as the entorhinal cortex, temporal lobe, hippocampus as well as the posterior cingulate and lateral parietal lobules will be identified using standard Harvard-Oxford Cortical and Subcortical atlas. CBF values will be compared in these regions between the 3 groups. The region of interest approach can dilute effects that are smaller than the size of the region of interest. Therefore, we will also perform permutations testing in FSL to evaluate voxel-wise CBF differences between group. In order to ensure that the voxel-wise outcomes are not mere chance, we will impose strict family-wise error correction for multiple comparisons. Blood flow data will be standardized to ml/100g/min, as per ASL protocols.

Statistics: From these images we will obtain measures on global blood flow (ml/100g/min) as well as regional blood flow in pre-defined regions (i.e. right temporal lobe). We will utilize standard statistical models to compare the 1, 2, 3, hour ASL to the baseline ASL to ascertain what time point produces the most robust change result. This will help cut down on the signal-to-noise ratio of the data as participants will serve as their

own control, in a repeated measures design. We will also compare total and regional ∆CBF by E4 status to detect whether patterns are different between E4 carriers and non-carriers (treatment*E4 effect).

Summary: Data from our laboratory consistently identifies that E4 carriers, who are at higher risk for AD, show paradoxical improvement after high fat feeding. We wish to explore this finding further using state-of-the-art MRI imaging to assess blood flow pattern responses in E4 carrier and non-carrier groups. With this project we will determine the most optimal time point for detecting post-lipid ∆CBF, as well as determine which regions of the brain respond to HFF and whether any regions differ by E4 status. With these types of studies, we hope to gain a more in-depth understanding of how HFF exerts influence on brain function and metabolism.