Arterial spin labeling reproducibility and potential for predicting hemodynamic alterations in older adults at risk for Alzheimer’s disease

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Introduction. Noninvasive MRI approaches capable of assessing tissue-level modulations in cerebral hemodynamics hold significant potential for gauging disease severity and progression in patients with, and at-risk for, Alzheimer’s disease (AD) (1). More specifically, while much is known regarding amyloid beta (Aβ) plaque deposition and structural changes in AD, comparatively less is known regarding possible hemodynamic and metabolic precursors to these changes (2). Increasing data suggest that chronic hyperperfusion and related oxidative stress may contribute to AD risk (3), but important gaps remain in our knowledge of how such factors relate to cognitive decline and disease onset. The critical barrier to understanding these questions lies with a lack of (i) noninvasive methodology for quantitatively and reproducibly assessing hemodynamics in cortical and subcortical structures and (ii) longitudinal and multi-component studies capable of tracking the relationship between cognitive performance, hemodynamic changes, and tissue atrophy over time. Here, we have implemented a customized arterial spin labeling (ASL) sequence specifically capable of assessing cerebral blood flow (CBF), or the rate of blood delivery to tissue, simultaneously in cortical and subcortical structures. The purpose of this study was twofold: First, to demonstrate reproducibility of ASL CBF measurements in brain regions implicated in AD. Second, to perform a battery of neuropsychological testing in conjunction with CBF measurements in control, AD risk (family history) and mild cognitive impairment (MCI) volunteers to assess the extent to which regional CBF correlates with cognitive performance. Results demonstrate that modified ASL protocols can assess regional CBF in multiple subcortical structures with high reproducibility and identify trends between CBF and cognitive performance in volunteers in pre-clinical stages of AD.

Methods. Experiment. All participants provided informed, written consent and were scanned at 3T (Philips) using body coil transmission and 8-channel array reception. Reproducibility Study. A pseudo-continuous ASL (pCASL) protocol was optimized for labeling duration (LD), inversion time (TI), spatial resolution and signal-to-noise ratio (SNR). Reproducibility of this optimized approach (LD/TI/TE/TR=1650/1650/13/4000 ms; spatial resolution=3.5x3.5x7 mm3; slices=15; bipolar crusher gradients) was assessed by scanning healthy young volunteers (n=7; age=29+/−6 yrs) twice in sequence with standard T1-weighted MPRAge MRI (1x1x1 mm3); CBF reproducibility was assessed in cortical and subcortical regions using standard intraclass correlation coefficient (ICC) procedures. Patient Study. Older adults (n=26; age=66+/−6 yrs) with no family history of AD (n=10), family history of risk but no clinical symptoms (n=10), and MCI (n=6) were scanned with the same protocol as above. Analyses. Each participant’s hippocampal volume size (FMRIIB Automated Segmentation Tool, FAST) was calculated and CBF was quantified within the subject-specific hippocampus mask. Genetic (APOE4) and cognitive testing were also conducted on each participant. The cognitive testing was conducted using the Mini Mental State Exam (MMSE) (4) and Consortium to Establish a Registry for Alzheimer’s Disease Immediate Recall (CERAD Immediate) (5). The CERAD word list memory test was of particular interest in testing participants’ immediate recall ability. Subjects were shown a set of 10 words and asked to immediately recall the words. This procedure was repeated over 3 trials, with a score of 30 representing perfect recall. This test is thought to assess hippocampal function, with lower scores denoting poorer encoding and hippocampal functioning.

Results. Reproducibility Study. Healthy young adults showed high CBF reproducibility in grey matter (ICC=0.83; P<0.03) and hippocampus (ICC=0.80; P=0.03). Fig. 1 shows voxel-wise reproducibility between Scan 1 and Scan 2 of a representative volunteer. Patient Study. Fig. 2 shows the hippocampal volumetric analysis between the three older adult groups demonstrating that the MCI group has lower volume than both the at-risk and control groups (P=0.05, error bars denote standard deviation). Fig. 3 displays the relationship between CBF and CERAD score for grey matter (a) and hippocampus (b). Note that all groups display a positive correlation between grey matter CBF and CERAD score. However, a different trend between hippocampus CBF and CERAD score is observed between groups: MCI patients exhibit a positive trend between CBF and CERAD score, whereas this trend is reversed for controls and at-risk volunteers.

Discussion. These data provide insight into the relationship between regional CBF and cognitive performance in older adults at-risk for AD. We observed positive relationships between cortical CBF and cognitive performance in all volunteers, but an inverse trend between hippocampus CBF and cognitive performance in at-risk and control participants. Interestingly, hyperperfusion (6) and hypoperfusion (3) have both been reported in preclinical onset of AD. We hypothesize that in the hippocampus, elevated CBF (which we find to inversely correlate with cognitive performance (CERAD)) may be a marker of less efficient encoding, requiring increased hemodynamic recruitment. However, once symptoms of MCI begin, this trend is reversed whereby better encoding is coupled to an increase in CBF. The mechanism of this overcompensation could be due to hippocampus excitoxicty and/or poorer encoding efficiency, both of which would alter CBF and possibly elevate hemodynamic demand (6). Better understanding the mechanistic origins of these phenomena should be possible by using pCASL in conjunction with molecular imaging approaches in a larger cohort of patients, which is an ongoing investigation in our lab.