Multi-modal MRI analysis for assessing memory impairment in the early stages of AD

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INTRODUCTION: Alzheimer's disease (AD) is a neurodegenerative condition characterized by a pre-clinical stage with hypothesized, yet unproven, vascular and metabolic changes in brain regions such as the posterior cingulate (PCC), default mode network (DMN) and hippocampus (HF)[1,2]. It has been shown that abnormal baseline BOLD synchrony in DMN and HF is consistent with poor performance during memory encoding[3]. Furthermore, individuals with mild cognitive impairment (MCI) suffer from memory and cognitive dysfunction, similar to AD patients, and may eventually progress to AD[2,4], but identifying which patients progress remains difficult. Currently Aβ plaques[3], which are prevalent in AD, are not reliably detectable with MRI. However, Aβ plaque deposition has been associated with reduced neuro-vascular coupling, inflammation and decreased vascular response[3], which can be interrogated with multi-modal MRI approaches. More specifically, subjects with familial risk of AD and those with MCI show increased baseline synchrony or task dependent activity, hypothesized to represent compensatory hemodynamic mechanisms[2]. Here, we employ multiple MRI techniques to characterize baseline hemodynamic changes in older healthy controls, adults at familial risk of AD and adults with MCI to achieve a multi-faceted comparison of the preclinical pathology of AD. We performed baseline BOLD MRI[5] and cerebral blood flow (CBF)-weighted pseudo-continuous arterial spin labeling (pCASL)[6], in conjunction with cognitive testing, to quantify differences in functionally eloquent regions implicated in AD in subjects with varying AD-risk and cognitive performance as evaluated by Consortium to Establish a Registry for Alzheimer's Disease (CERAD) scores for verbal fluency and recall.

MATERIAL AND METHODS: All volunteers provided, informed written consent in accordance with the local IRB. *Experiment:* 21 subjects (8 controls, 7 subjects at familial risk of AD and 6 MCI subjects) were studied using a single-shot, echo-planar imaging (EPI) sequence to quantify BOLD contrast at 3T (Philips). 35 slices were acquired at a spatial resolution of 3 x 3 x 4 mm^3 and TR/TE = 3000/35 ms (140 dynamics). For evaluating CBF, a pCASL scan with 15 slices (3.5 x 3.5 x 7 mm^3) at TR/TI/TE = 4000/1625/13 ms was acquired. Whole-brain T_1-weighted (1 mm^3 isotropic) structural images were also acquired for registration purposes. *Analysis:* BOLD: Preprocessing steps included high frequency noise removal, baseline drift correction, smoothing (FWHM=3 mm), and motion correction in FSL. BOLD data were registered to a 2 mm resolution MNI template. Baseline synchrony was evaluated using multi-subject temporal concatenation of the time courses and independent component analysis (ICA)[7] in FSL. The DMN was identified from the ICA components and a region of interest (ROI), corresponding to the PCC, was identified from the Harvard-Oxford Cortical and Sub-Cortical Atlas in FSL. ROIs were also identified for the left and right HF. ROI-based connectivity analysis was performed to evaluate the synchrony of BOLD fluctuations between HF and PCC using FEAT[8]. The hippocampal connectivity (Z score) to other brain regions was normalized by the maximum Z score for the individual subject, to reduce artificial inter-subject variability for comparison. In the PCC, baseline synchrony measures (Z scores), baseline CBF (ml/100g/min) and relative synchrony strength of PCC with HF were compared. ASL: Difference maps were calculated and absolute CBF (ml/100gm/min) was computed upon application of the flow-modified Bloch equation. The same ROIs were used for BOLD and ASL comparisons.

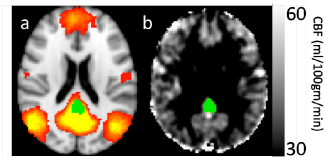

Figure 1*: a. DMN network, b. corresponding CBF map. Green ROI shows PCC region for analysis*

RESULTS AND DISCUSSION: ***Figure 1*** shows a representative slice showing the DMN overlaid on the MNI template and the corresponding CBF map. Baseline CBF and synchrony in the DMN exhibit an inverse correlation in controls in the PCC as shown in ***Figure 2***. Similar inverse correlations[9,10] have been observed in other studies, especially in healthy older adults[10]. Therefore, it is possible that highly synchronous, intact and efficient brain networks require lower CBF thus giving rise to this inverse correlation. Here we show that this inverse correlation is weakened in subjects at risk of AD and is positive in MCI subjects. While the average Z scores for the BOLD fluctuations in the PCC decreased in the at-risk and MCI subjects compared to the controls, the CBF increased in the at-risk group and decreased in the MCI group. Compensatory mechanisms could result in an increased CBF in the at-risk population yet impaired synchrony within the PCC could result in decreased BOLD synchrony. Decreased baseline CBF, and possibly decreased neural activity, in the MCI subjects may likely reduce the baseline BOLD fluctuation synchrony in the MCI subjects. Additionally, correlation of the CERAD I (immediate recall) scores to the left and right HF connectivity to the Pre/PCC region was evaluated. Significant, negative correlation (Figure 3) was observed with PCC connectivity to the left HF ($r = -0.35$, $p < 0.05$), while the positive correlation, measured for the right HF was insignificant. In ***Figure 3***, we show connectivity of left HF to the PCC. The at-risk subjects had a significantly stronger synchrony between the left HF and PCC ($p<0.05$). The MCI subjects showed lower synchrony between left HF and PCC compared to at-risk subjects but higher compared to controls. However, MCI subjects had CERAD I scores significantly lower (15.5±0.7, $p<0.05$) than controls (21.4±0.6) and at risk subjects (20.9±0.5). It is possible that the increased connectivity of the left HF to PCC in the at-risk subjects reflects an initial compensatory response. On the other hand, the lower connectivity of left HF to the PCC in the MCI subjects may be indicative of failure of such compensatory mechanisms in early stages of cognitive decline. Further, these data suggest that right HF connectivity to the PCC may not be critical for verbal memory recall, as tested by CERAD I.

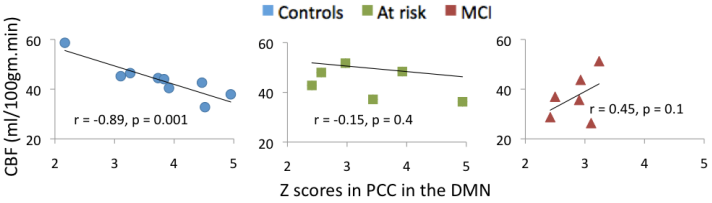

Figure 2*: CBF and BOLD fluctuations in the PCC*

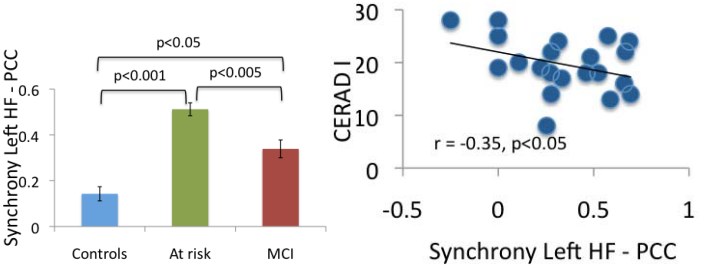

Figure 3*:Left: Left HF connectivity to the PCC and (Right) relation to CERAD I*

CONCLUSION: We have employed multi-modal MRI analyses approaches to detect differences in preclinical stages of AD that may contribute to memory and cognitive dysfunction. We assessed the correlation between CBF, baseline BOLD fluctuations in the PCC, and the HF synchrony with PCC. Results of this study suggest that multi-modal MRI strategies to characterize neurological disorders and their relation to neuropsychological evaluations may have relevance for AD diagnosis and risk assessment.

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