Feasibility of Detecting Preclinical Hippocampal Neuronal Cell Loss in Subjects Destined to Develop Alzheimer's Disease

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Purpose: Alzheimer's disease (AD) is an increasing neurodegenerative disease in our aging population that costs the United States healthcare system around $170 billion dollars annually. This disease is the cause of most dementia in the elderly and is a progressive disease in which the pathophysiology begins in the hippocampus as neuronal cell loss with deposition of extracellular amyloid protein (plagues) and excessive polymerized tau protein within neurons (neurofibrillary tangles). This process starts decades prior to the clinical expression of the disease that presents clinically as memory loss. Ultimately, the pathology spreads to the temporal and parietal areas of the brain and clinically to all cognitive domains. There are no cures or long lasting interventions for this devastating disease. However, the early changes in cell density offer an opportunity for detecting preclinical disease. If this stage of the disease can be detected and the progression followed objectively, early interventions can be designed and evaluated without the use of clinical disease as an outcome measure. We have used quantitative sodium MRI at 3.0 and 9.4 Tesla to examine the sensitivity of the tissue sodium concentration (TSC) bioscale and its related tissue cell fraction (TCF) bioscale [1] for detecting cell density changes in the hippocampal regions of subjects with mild probable AD and mild cognitive impairment (MCI) that can progress to AD.

Materials and Methods: IRB and FDA approved protocols with informed signed consent were used for human studies at 3.0 and 9.4 Tesla. The subjects underwent extensive neuropsychological evaluation to evaluate their cognitive function that has been summarized in the mini mental status examination (MMSE) scores where 30 is normal and below 28 represents declining cognitive function. Quantitative flexible twisted projection imaging (flexTPI) [1] was used to measure TSC and TCF in normal elderly subjects (N=3), in subjects with mild AD (N=2), and subjects with MCI (N=1). Quantification was performed with a three-point calibration phantom matched to the same electrical loading of the sodium RF coil as the human head. Previous results have shown that the error of repeated independent measurements is less than 4% [1]. The hippocampal TSC and TCF were sampled using COMPASS software that cross registers aligned proton and sodium images to allow definition of the hippocampus and motor cortex from the proton images on the corresponding sodium bioscale to avoid contamination of tissue measurements from cerebrospinal fluid (CSF) in the adjacent sulci (Figure 1).

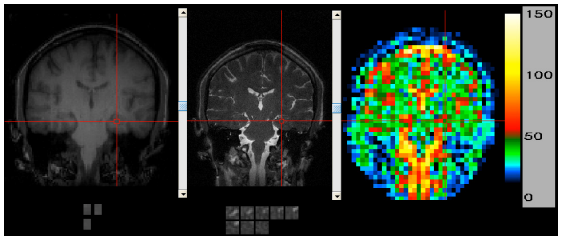

Figure 1. COMPASS software cross-registers T1-weighted (left) and T2-weighted (center) proton images to the coronal TSC bioscale (right) to guide voxel selection in the left hippocampal region of the bioscale.

Results and Conclusion: Table 1 shows hippocampal and motor TSC, TCF and TCF index values of the individual subjects across a range of MMSE scores. Whereas the values for motor cortex are stable, there is a direct correlation (R^2=0.91) between the declining MMSE scores and decreasing TCF in the hippocampus. This is further supported by the use of the TCF index using motor cortex values where the motor cortex is not involved in AD. The 9.4 Tesla result is interesting as the greater sensitivity at higher field allowed improved resolution, possibly decreasing CSF contamination of the measurements. Although this is a small number of subjects, the results suggest that further studies are warranted.

Group	Field (Tesla)	MMSE (score)	TSC-Hippo (mM)	TSC-Motor (mM)	TCF-Hippo (fraction)	TCF-Motor (fraction)	TCF index (Hippo/Motor)
pAD	3.0	20	57.5	34.9	0.62	0.80	0.77
pAD	3.0	24	42.3	34.0	0.74	0.81	0.91
MCI	3.0	28	38.6	33.3	0.77	0.82	0.95
Elderly Control	3.0	30	36.2	30.7	0.79	0.84	0.95
Elderly Control	3.0	30	36.2	33.9	0.79	0.81	0.98
Elderly Control	9.4	30	34.8	35.2	0.80	0.80	1.01

Reference: **[1]** Lu A, Atkinson IC, Claiborne T, Damen FC, Thulborn KR. Quantitative sodium imaging with a flexible twisted projection pulse sequence. Magn Reson Med 2010 63(6):1583-93.

The authors gratefully acknowledge financial support from the PHS RO1 CA CA1295531. This work was funded in part by the Chicago Biomedical Consortium with support from The Searle Funds at The Chicago Community Trust.