Early marker for Alzheimer's disease: Hippocampus T1rho ($T_{1\rho}$) estimation

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Introduction:

Alzheimer's disease (AD) is a most common form of neurodegenerative disorder in elderly that results in progressive memory loss and cognitive decline. The appearance of senile plaques and neurofibrillary tangles is the neuropathological hallmarks of AD[1]. Autopsy studies have shown that the hippocampus to be affected by AD pathology early in the disease process, with approximately 20–50% loss of neurons by the time individuals is moderately affected[2,3]. As a result imaging studies have focused on this region in order to monitor the early changes during the disease progression. The goal of research in this area is therefore to develop highly specific and sensitive methods capable of identifying the subjects in the early stage who are in progress to AD. Neuroimaging markers provide an alternative and objective assessment of progression of AD. An alternate contrast mechanism is T1rho ($T_{1\rho}$), the spin lattice relaxation time constant in the rotating frame, which determines the decay of transfer magnetization in the presence of "spin-lock" radio-frequency field[4]. In biological tissue exchange between protons in different environments is expected to contribute $T_{1\rho}$ relaxation. The molecular process that occurs in the milliseconds range influences $T_{1\rho}$ relaxation. Earlier, $T_{1\rho}$ has been used to delineate brain tumors, characterize breast cancer tissue, and monitor the level of cartilage degeneration[5-7]. The current study was performed with an aim to measure base line $T_{1\rho}$ in hippocampus in the brain of AD, MCI and Control and to determine whether $T_{1\rho}$ value show any significant difference between these cohorts.

Materials and Methods:

Patient Selection: The Institutional Review Board approved the study protocols. In the current study, we included 49 AD patients (mean age±SD = 76.8±9.1 years), 48 MCI patients (mean age±SD = 71.93±8.7 years), and 31 age-matched controls (mean age±SD = 70.2±9.4 years). The Mini-Mental State Examination (MMSE) was used as a measure of cognitive function. Diagnoses of MCI and AD were made according to the criterion defined elsewhere[8,9]. The control group consisted of patients, who presented to our memory clinic with subjective complaints, and underwent exactly the same diagnostic work-up as the MCI and AD patients.

MRI protocol: With informed consent all these patients underwent a standard MRI protocol on a 1.5 Tesla clinical scanner using the vendor-supplied head coil. For $T_{1\rho}$ MRI, a fluid-attenuated $T_{1\rho}$ pre-encoded Turbo Spin-Echo pulse sequence was used (7). The imaging parameters were: TE/TR = 12/2000 ms, TSL (duration of spin lock pulse) = 10, 20, 30, 40 ms, with a spin lock frequency of 500Hz, slice thickness = 2mm, FOV = 22 cm, Matrix size=256x128, bandwidth= 130Hz/pixel, echo train length = 4 and inversion time (TI)=860 ms. Immediately after $T_{1\rho}$ MRI, the entire volume of each subject's brain was imaged in the coronal plane using a T_1-weighted 3D volumetric MPRAGE pulse sequence with 124 continuous slices. The parameters were TE/TR= 3.5 ms/3000 ms, slice thickness= 1.2 mm, FOV of 24 cm and 192 phase encode steps, and flip angle =8°.

Data Processing: $T_{1\rho}$ maps were generated by fitting each pixel's intensity as a function of the duration of the spin-lock pulse (TSL) by a linear least-squares algorithm[4]. Pixels whose intensities correlated poorly (R^2<0.95) with the fitting equation were set to zero. Pixels outside of the brain were also set to zero. $T_{1\rho}$ values were automatically calculated from the left and right hippocampus region by an algorithm described previously[4]. For hippocampus segmentation a previously developed method was used to partition the volumetric MPRAGE scans into 92 ROIs incorporating all major cortical and sub-cortical regions[10]. This method deforms MRI scans of different brains into anatomical co-registration with each other, and into co-registration with a standardized template. The template's labels are then transformed to individual scans by applying the elastic transformation that was found to co-register the respective images.

Statistical analyses: For statistical analysis $T_{1\rho}$ value from left and right side were averaged for hippocampus. One Way Analysis of Variance (ANOVA) using Bonferroni post-hoc multiple comparisons was performed to compare $T_{1\rho}$ value among the different cohorts. Pearson correlations between $T_{1\rho}$ values versus age and between $T_{1\rho}$ versus MMSE score were performed.

Results:

MMSE examination score were 29.03±1.13 in control, 24.72±2.93 in MCI and 19.34±6.04 in AD. Figure 1 shows $T_{1\rho}$ maps of the control, MCI and AD. The pixels with higher $T_{1\rho}$ in the hippocampus of AD are also apparent from the $T_{1\rho}$ maps (Fig. 1). The mean hippocampus T1ρ values in controls, MCI and AD were 88.5±1.9 ms, 95.1±2.1 ms and 101.8±1.6 ms. One way ANOVA showed that $T_{1\rho}$ was significantly changed (p=0.000) between the groups. Bonferroni multiple comparisons showed that $T_{1\rho}$ was significantly increased both in AD (p=0.000) and MCI (p=0.037) cohorts compared to control (Table 2). A significant increase in $T_{1\rho}$ was observed in AD (p=0.032) compared to MCI (Table 1). In AD the hippocampus $T_{1\rho}$ was increased by 13% over control while it was increased around 7% in MCI over control. The hippocampus $T_{1\rho}$ in AD patients was increased by 6% over MCI. No significant correlation was observed between $T_{1\rho}$, age and MMSE scores.

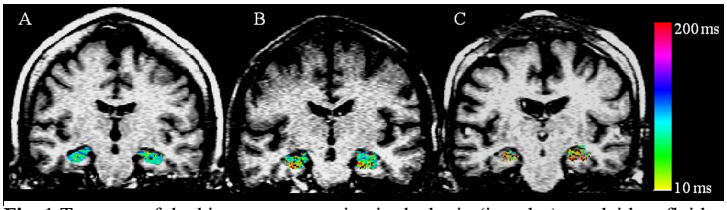

Fig. 1 $T_{1\rho}$ maps of the hippocampus region in the brain (in color) overlaid on fluid-attenuated $T_{1\rho}$ MRI of control (A), MCI (B) and AD patient (C). Pixels with higher $T_{1\rho}$ (red) are more prominent in hippocampus of AD patient.

Group	Group	Mean difference	p value	95 % CI	
				LB	UB
Control vs	MCI	-6.7	0.037*	-13.73	0.29
	AD	-13.3	0.000*	-20.33	-6.36
MCI vs	AD	-6.6	0.032*	-12.80	-0.44

Table 1: Bonferroni multiple comparisons

Discussion:

In the current study, significant increased $T_{1\rho}$ in hippocampus of MCI and AD patients was found compared to control. In AD the hippocampus $T_{1\rho}$ was significantly increased over MCI. It has been shown that increased $T_{1\rho}$ signal in AD patients is associated with the plaque burdens[11]. Even after significant difference in $T_{1\rho}$ between three cohorts, some of the MCI and control individuals showed high $T_{1\rho}$ value in the range of AD pathology. This suggests that the MCI and control individuals with higher $T_{1\rho}$ might have the AD like pathology which cannot be depicted during the course of clinical observation, which are the criteria for discriminating the individuals in their respective stage. In the current study, no correlation between MMSE and $T_{1\rho}$ also suggests that clinical cognitive score is not sufficient to assess the underlying pathological changes, while increase in $T_{1\rho}$ is due to the increased plaques burden. In the current study no correlation between age and $T_{1\rho}$ suggesting that the change in $T_{1\rho}$ is due to an underlying pathology. It remains to be seen, perhaps by a longitudinal study, whether hippocampus $T_{1\rho}$ in subjects with isolated memory impairment predicts a higher risk of developing AD, or conversely is only related to the presence of memory deficit. We conclude that higher hippocampus $T_{1\rho}$ value in AD patients might be associated with the increased plaques burden and the individuals (MCI and controls) with higher hippocampus $T_{1\rho}$ value may have the more probability to convert into AD in future. Once $T_{1\rho}$ meets the diagnostic criteria of AD in early stage, it can be used as a biomarker in the development of various putative therapeutic agents for the treatment of AD.

References:

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