Multi-slice 3T T1ρ Quantitative Imaging as an Early Biomarker of Alzheimer Disease: Preliminary Voxel-based Analysis in Controls, At-risk and MCI Subjects

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Background: Accurate and early diagnosis of Alzheimer Disease (AD), the most common form of senile neurodegeneration has been particularly challenging. To date, there has been no accurate cognitive marker to identify AD in its early stages. Neuritic plaques and tangles are often neural hallmarks of the disease. Neuroimaging, being an alternate and possibly more objective assessment of AD, has shown promise in this arena. The aim of this study is to evaluate the non-invasive contrast mechanism, T1ρ (T1 in the rotating reference frame), which is capable of probing molecular environment and chemical exchange rates, in patients at-risk for AD. This method has been previously reported to sucessfully identify significant differences in macromolecular content by capturing differences in T1ρ relaxation times using single slice or regional imaging in AD and Parkinson disease patients at 1.5T (Haris et al., 2009, 2011; Borthakur et al., 2008). In this study we aim to 1) perform quantitative multi-slice T1ρ mapping on a 3T scanner and 2) assess correlations between regional T1ρ and a battery of neuropsychological memory tests in a group of cognitively normal elderly controls (CTL), healthy individuals at risk (AR) due to family history of AD , and individuals with mild cognitive impairment (MCI) . The goal is to evaluate T1ρ MRI as a robust *early* non-invasive biomarker for AD, which could then be used as a possible alternative to invasive PET PiB imaging for plaque identification.

Figure 1

Methods and Materials: The study included a total of 14 subjects (6 CTL, 4 AR and 4 MCI), who provided informed, written consent and were scanned at 3T (Philips) using a 8-channel array reception coil and body transmit coil. Subjects were group matched on age and sex. A battery of cognitive tests including the mini-mental examination (MMSE), CERAD delayed recall (CERAD-D) and TRAIL making test (TMT-B) were conducted on each participant. The TMT-B assesses general cognitive flexibility with a higher score indicating more cognitive dysfunction whereas the CERAD-D focuses on hippocampal function with a higher score representing better encoding. For $T_{1\rho}$ -weighted images, a fluid-attenuated $T_{1\rho}$ pre-encoded Turbo Spin-Echo pulse sequence was used. The imaging parameters were: TE/TR = 10/2700 ms, T_{SL} (duration of spin-lock pulse) = 20, 50 and 80 ms, with a spin-lock frequency of 550 Hz, B_1 = 13.5 µT, slice thickness = 5 mm, slices = 12, voxel size = 1.83 x 1.83 mm covering key temporal and frontal regions affected in AD (See figure 2). In addition, for comparison and validation purposes, we also acquired conventional T_2-weighted images in the same space as above at TEs of 15, 30, 45, 60, 75 and 90 ms. $T_{1\rho}$ maps were generated by fitting the log of each pixel's intensity as a function of

Figure 2

the duration of the spin-lock pulse (T_{SL}) using a linear least-square algorithm implemented in SPM8. Similarly, a linear fit was computed fitting all odd echoes to obtain a quantitative T_2 map for each individual. All images were spatially normalized by co-registering to a standard template in MNI space. Images were then masked using an *a priori* gray matter template. A statistical random-effects one-way ANOVA model was used to test for between-group differences in $T_{1\rho}$ on a voxel-wise basis. We also performed voxel-wise linear correlations to assess associations between variations in $T_{1\rho}$ values and TMT-B, CERAD-D scores across all subjects.
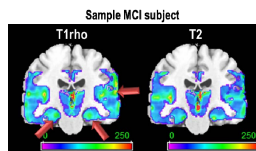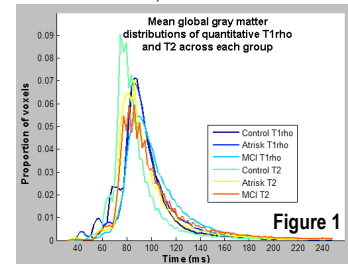
Results: MMSE scores were significantly different (p=0.001) between CTL (Mean±SE = 29.8±0.17) and MCI (Mean±SE=27.6±0.3) but not (p=0.85) between CTL and AR. Global gray matter $T_{1\rho}$ histogram distributions (Figure 1) indicate that CTL and AR had similar distributions with very subtle variations; however the MCI group had a higher variance and marked shift in peak value (indicating longer relaxation values) compared to CTL and AR. Global histograms also demonstrated that T_2 values were lower (shifted to the left) in all three groups compared to $T_{1\rho}$, as previously shown in other studies implementing regional analyses (Haris et al., 2009). Sample spatial maps (Figure 2) from an MCI subject show a larger range of $T_{1\rho}$ estimates compared to T_2 (especially in regions indicated by arrows). Given the similarity in distributions between CTL and AR, the groups were collapsed into a single group for estimating between-group differences in $T_{1\rho}$. Results indicated that several AD-relevant regions showed a lengthened $T_{1\rho}$ in MCI subjects compared to CTL+AR. Figure 3 shows the significant group differences thresholded at an unadjusted p<0.01 significance level. A few critical regions related to AD pathology are highlighted along with their $T_{1\rho}$ group estimates. The study also found multiple disease-relevant regions positively associated with TMT-B. Regions positively associated with TMT-B were superior temporal gyrus, transverse temporal gyrus, posterior cingulate, putamen, anterior cingulate, middle frontal gyrus, inferior frontal gyrus, parahippocampal gyrus, and middle temporal gyrus. Similarly, $T_{1\rho}$ values in the parahippocampus/hippocampus, superior/middle temporal gyrus and middle occipital gyrus correlated negatively with CERAD-D scores across all subjects.
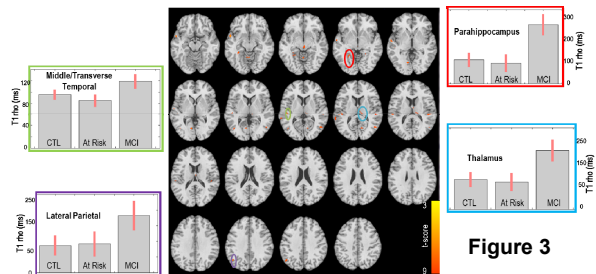

Figure 3

Discussion/Conclusion: We were able to confirm 3T $T_{1\rho}$ estimates in the context of prior reports (Borthakur et al 2004; Haris et al 2009) in the literature and with reference to conventional T2 images acquired on the same subjects. Using a multi-slice scan acquired at 3T, this preliminary study identified several AD-relevant regions with significantly increased $T_{1\rho}$ estimates in MCI subjects. In addition, we identified associations between $T_{1\rho}$ estimates and TMT and CERAD scores in multiple brain areas known to be compromised in AD, underscoring the potential usefulness of $T_{1\rho}$ imaging as an early biomarker for AD pathology.