

3T Automated High Resolution MTR in Alzheimer's Disease and Healthy Elderly Subjects

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INTRODUCTION: Study of hippocampus and subcortical brain structures are particularly imperative due to their early involvement in various progressive neuronal diseases including Alzheimer's disease (AD). Sensitive and reliable hippocampal and subcortical measurement requires high resolution imaging because of the small size of the regions of interest (ROIs). We developed a comprehensive automated high resolution magnetization transfer (MT) workflow at 3T that entirely eliminates manual ROI placement. Relative to manual approaches, this technique (Fig 1) removes operator induced errors thus standardizing quantification and improving the measurement reliability (Wu 2011), which may contribute to both longitudinal and multi-center studies. While MT may be more sensitive to subtle brain alterations at higher field strengths, its clinical utilities have not been well established at 3T. In this study, various MT ratio (MTR) measurements including histogram metrics and mean MTR, derived from this novel automated post-processing technique, were evaluated and compared in mild AD patients and an age-matched control group.

METHODS AND MATERIALS: **MRI Acquisition:** 9 mild AD (6 males, 3 females, mean age: 76.6 ± 5.6 yrs, MMSE: 24.9 ± 2.5) and 11 normal aging subjects (8 males, 3 females, mean age: 67.9 ± 4.6yrs; MMSE: 29.1 ± 0.9) were scanned using a 3 Tesla Siemens system (MAGNETOM Verio, Siemens Healthcare, Erlangen, Germany). High-resolution MT images were obtained using a three-dimensional gradient echo sequence (TR/TE/FA 30ms/4ms/10°, spatial resolution = 1.0 x1.0 x1.2 mm³). Images were acquired with and without MT (saturation pulse applied for 9.98 ms with flip angle of 500° and 1200 Hz offset from water resonance). Structural MP-RAGE T1-weighted images were acquired using the ADNI protocol (TR=2300ms, TE=2.94ms, TI=900ms, flip angle 9°, 160 sagittal 1.2mm thick slices, matrix = 256x256 with field of view of 256mm, resulting in a voxel size of 1.0 x 1.0 x 1.2mm³). **Image Analysis:** Pixel-by-pixel MTR maps were derived using custom software with standard equation on a Linux workstation. MTR was calculated as $(M_0 - M_{SAT})/M_0$ where M_{SAT} and M_0 represent voxel signal intensity with and without MT, respectively. In order to produce ROI measurements without manual placement, an automated segmentation was incorporated using FreeSurfer. The registration coregistered MTR maps to segmented hippocampus and other brain structural masks. Mean MTR and histogram MTR metrics were evaluated for the control and AD groups. Mean MTR was computed and defined as the average MTR of all voxels in the 3D volume of interest. Normalized histograms of MTR were automatically plotted using a customized Matlab program.⁵ Histogram peak height, peak location, mean, and median were derived. **Statistical Analysis:** The MTR measures calculated for the mean and the histogram in specific regions of interest were compared in the two groups. A Shapiro-Wilks test was used to assure that the normality assumption was fulfilled and a two-sample t-test was then performed to detect the between-group difference. The quantitative MTR measurements were examined for patterns of relationship to MMSE, the severity of cognitive impairment and deficits in specific cognitive functions by calculating the Pearson correlation coefficients (rho, for ratio-scaled variables) and Spearman correlation coefficients (for ordinal-scaled clinical ratings). All statistical tests were two-tailed and were executed using Matlab (Matlab, R2011a, Natick, MA), and statistical significance reached when p<0.05.

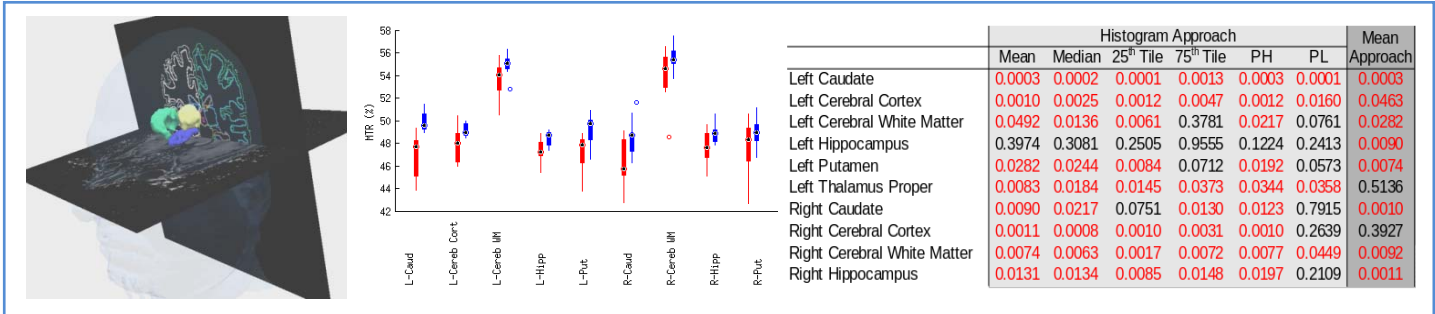


Fig1. Automated MTR measurement based on segmentation. This figure illustrates: 3D rendering of the hippocampus (blue) and caudate (green and yellow). The segmentation mask (color map on coronal view), and the MTR map (gray scale on axial view) were reformatted.

Fig2. Box plot of MTR values obtained from the mean approach (Blue: control group, Red: AD group). Significant differences (p<0.05) were found for the regions showing. Notice that in each case, the MTR value is lower for the patients group than that of the controls.

Table 1. Group t-test of MTR metrics (histogram approach and mean approach) between AD and normal control. P<0.05 are highlighted in red.

as a covariate indicated significantly lower MTR in AD patients (p<0.05) for the bilateral caudate, hippocampus, putamen, cerebral cortex and white matter (Table 1). As shown in the box plot (Fig 2), the left caudate yielded the best differentiation between the AD group and the control group, as most AD patient had a lower MTR value compared to that of the normal group. Similar and complimentary results were indicated for MTR metrics derived with the histogram approach and the mean approach in the detection of abnormalities in brain regions (Table 1). There was no positive correlation detected between MTR and the severity of cognitive impairment MMSE scores.

DISCUSSION: Various studies of progressive neurological diseases have demonstrated MTR sensitivity to subtle histological changes that are not otherwise detectable with conventional MR. Application of MT in AD has been limited to only a few studies (Ramani 2006) and none have used automated volume of interest measurements based on high resolution MT at 3T. Our investigation detected subtle brain changes in the hippocampus, caudate, putamen, cerebral cortex and white matter that differentiate the AD from the control group. MRI studies in AD have been mainly focused on medial temporal and cortical structures, but amyloid and tau deposits also accumulate beyond the hippocampus and caudate atrophic changes was indicated in AD study of 400 subjects (Madsen). The majority of MT studies have been performed at 1.5T. Our data demonstrates significant MTR differences between AD and control groups, and future work can assess the effect of improved spatial resolution on disease sensitivity in detection of subtle brain alterations that complement other MRI-derived measures of disease burden in AD. Our finding regarding the correlation between MTR and MMSE is in agreement with previous reports (Ridha 2007).

References: Ramani A. Quantitative MR imaging in Alzheimer disease. Radiology 2006. Wu Y. Comprehensive brain analysis with automated high-resolution magnetization transfer measurement. J Magn Reson Imaging. Ridha B.H. Magnetization Transfer Ratio in Alzheimer Disease: Comparison with Volumetric Measurements. AJNR 2007. Madsen, SK. Automated High Resolution localized MTR in Alzheimer's Disease and Healthy Elderly Subjects. Neurobio of Aging. 2010.