MTR at 3T in the Hippocampus – Validation of Automated Post-Analysis and Comparison of Quantification Metrics

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Introduction: Current research diagnostic criteria of Alzheimer's disease (AD) has been proposed to incorporate the size of hippocampus derived from MR volumetry.[1] However much of the hippocampal morphological changes occurs after microscopic changes take place. Magnetic transfer (MT) contrast using MR imaging is sensitive to subtle histological changes shown in progressive neurological diseases such as AD.[2] In addition to sensitivity, reliability and precision are crucial for any noninvasive imaging quantitative parameters in assessing disease substrates for both cross-sectional and longitudinal studies.[3] While MT may be more sensitivity to subtle brain alterations increases at higher field strengths, MT reliability has not been well-established at 3T. In this study, various MT ratio (MTR) measurements including histogram metrics and mean MTR, derived from a novel automated post-processing technique, were evaluated and compared to the more established volumetric measurements in the context of reliability and reproducibility.

Methods and Materials:

MRI acquisition: Eight healthy subjects (5 males, 3 females, mean age: 33yrs, range: 18-65) were scanned twice in an interval of one week. Images were acquired 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 = 0.93x0.93x1.2 mm^3). 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) and MTR was calculated as $(M_0\text{-}M_{SAT})/M_0$ where M_{SAT} and M_0 represent voxel signal intensity with and without MT, respectively. For volumetric measurements, 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 1.2mm^3).[4]

Image Analysis:

Pixel-by-pixel MTR maps were derived using custom software with standard equation on a Linux workstation. In order to produce brain regional measurements without manual placement, an automated segmentation was incorporated using FreeSurfer.[5]The registration was applied to align by coregistering MR maps to segmented hippocampus masks. This procedure was fully automated and required no operator intervention. Mean MTR and histogram MTR metrics were evaluated for reproducibility.[6] 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. Brain volumetric measurements of the hippocampus and white matter were derived using FreeSurfer.

Statistical Analysis: Between-time reliability was assessed using intraclass correlation coefficients (ICCs). A one-way random effects ANOVA model was performed by assuming each subject was randomly selected from a larger population of different set of two time points.[7] Between-time reproducibility was assessed using coefficient of variation (COV) for repeated measures.[8] Instrumental standard deviation (ISD) was computed to measure instrumental variation. Bland Altman analysis was used to estimate standard deviation of a single measurement and ISD is calculated as the root mean square value of the differences divided by 1.4.[3] Scatter plots were generated to illustrate reliability between two different scans.

Table1. Instrumental Standard Deviation	**Histogram**		**Mean**
Hippocampus	Peak Location	Median	Mean MTR
Left	0.99	0.83	1.03
Right	0.78	0.85	0.82

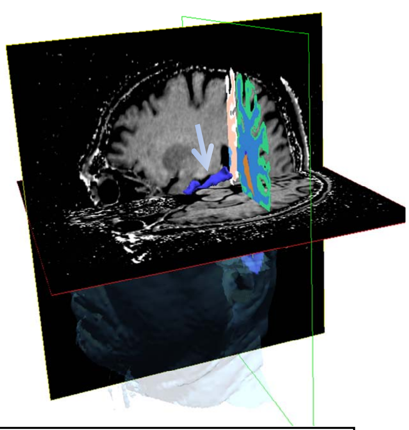

Fig 1. The MTR and volumetric measurement of the hippocampus based on automatic segmentation. This figure illustrates: 3D rendering of the hippocampus (light blue arrow), the segmentation mask (color map), and the MTR map reformatted for sagittal view (grayscale image). The facial 3D was generated to show spatial orientation.

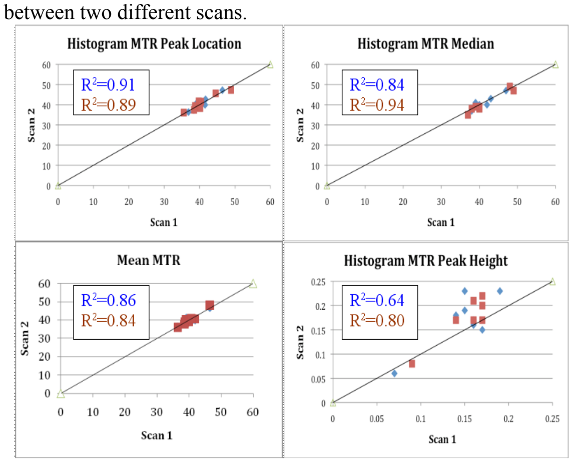

Fig 2. Scatter plots of scan-rescan reliabilities of MTR metrices of right and left hippocampal regions. (Blue→ right hippocampus, Red→left hippocampus)

Results: MTR measurements via the histogram approach provided reliable values. Among the different MTR approaches histogram median, peak location and mean MTR gave ICC's greater than 0.9 with a range 0.93-0.96. COV of these measures were all below 4% with a range 2.71-3.58%. ISD ranged 0.78-1.03 (Table 1). ICC of histogram peak height was below 0.7(range: 0.58-0.66) and COV was above 10% (range: 17.53-20.81%) reflecting relatively lower reliability and reproducibility. These results are visualized using the scatter plots in Figure 2. For the volumetric measurements of hippocampal size using automated Freesurfer segmentation, ICC's were between 0.95-0.97 with COV range 1.43-3.39.

Discussion: In this investigation MTR measurements using both histogram (median and peak location) and mean calculations provided excellent scan-rescan agreement indicating reliable measurements over time. On the other hand, peak height, a common MTR measure did not achieve acceptable reliability at 3T, which is consistent with previous findings at 1.5T.[9] These results suggest that mean, median and peak location are more reliable histogram measures than peak height for future longitudinal studies. Furthermore, overall the reliability of the MTR method is comparable to the volumetric approach. Future studies can examine the possibility that MTR changes precede morphological changes as this study suggests that both MTR and volumetric measurements of hippocampus can be used as reliable imaging tools in longitudinal investigations at 3T.

References: **1.** Gauthier S et al. 2008 *Lancet.* , **2.** Ramani A. 2006 *Radiology*, **3**. Tofts P. 2003 Quantitative MRI of the Brain **4.** Jack CR et al. 2008 *J Magn Reson Imaging*, **5.** Wu Y et al. 2006 *AJNR,* **6.** van Buchem MA et al. 1999 *Neurology,* **7.** Shrout PE and Fleiss J. 1979 *Intraclass correlations: Uses in Assessor Rate Reliability* **8.** McLaughlin SC et al. 1998 *The Value of COV in Assessing Repeat Variation in ECG Measurement* **9.** Ge Y et al. 2003 *AJNR.*