High resolution MTR at 3T using Automated Analysis Targeting Small Functional Brain Regions – A Validation Study on Normal Subjects

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Introduction: Obtaining reliable and reproducible measurements is essential for monitoring progression of chronic brain diseases. Magnetization transfer ratio (**MTR**) has been utilized as a sensitive, non-invasive neuroimaging modality for various brain disorders. However this approach has been primarily evaluated at 1.5T. Imaging at 3T would be advantageous because of the improved signal-to-noise ratio. The purpose of this study was to i) test a new high resolution MTR sequence at 3T; ii) determine the reproducibility of high-resolution MTR measurements at 3T; and iii)determine the feasibility of automated volume of interest MTR measurement in hippocampus and other small subcortical regions in comparison with manual convention. Stringent statistical testing was conducted using intraclass correlation coefficients (**ICC**s) coefficient of variation (**COV**) and instrumental standard deviation (**ISD**) [1,2]. While ICC is commonly used in medicine and psychology, it has a basic limitation for comparisons between centers because the value depends on the population variance. This investigation also estimated ISD, which is independent of subject type.

Method and Materials:

MR Image Acquisition: 9 healthy volunteers (6 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 ° and1200 Hz offset from water resonance). Structural T1-weighted images were acquired using the ADNI standard protocol [3].

Quantitative Analysis of MTR: ***MTR Maps*:** Whole brain pixel-by-pixel MTR maps (Fig1) were constructed on a Linux workstation using customized image processing software. MTR was calculated as $(M_0-M_{SAT})/M_0$ where M_{SAT} and M_0 represent voxel signal intensity with and without MT. Whole brain MTR maps for the second timepoint were spatially aligned to the baseline maps using FLIRT (FSL, FMRIB, Oxford, UK) [4]. ***Automated measurements*:** Automated segmentation was implemented on the structural MR using FreeSurfer [5]. Co-registration was applied to the structural MR and MT images. Volumetric segmentation masks for amygdale (**Amyg**), caudate (**Cau**), putamen (**Put**), hippocampus (**Hipp**), thalamus (**Thal**), genu and splenium (**Splen**) were projected onto the MTR maps to extract measurements (Fig 1). This procedure was fully automated and required no operator intervention. ***Manual measurements*:** ROIs (30 ~ $43mm^2$) were manually and independently placed on the spatially aligned MTR maps from two scanning sessions using MRIcro (www.mricro.com).

Statistical Analysis: Between-time reliability was assessed using ICC, COV and ISD for repeated measures. To compute the instrumental variation, Bland-Altman analysis was used to estimate the SD of a single measurement and ISD was calculated as the root mean square value of the differences divided by 1.4 [5]. For each anatomical region, the limit of agreement between twotimepoints was also calculated using the Bland-Altman method.

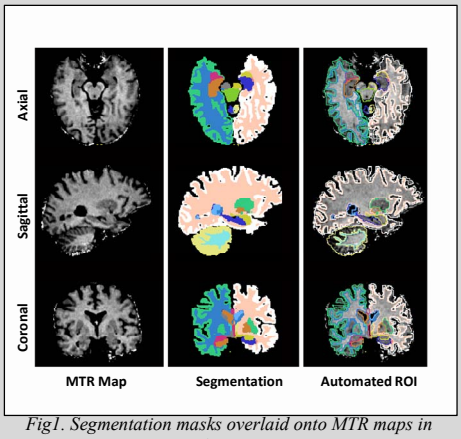

Fig1. Segmentation masks overlaid onto MTR maps in 3-plane views

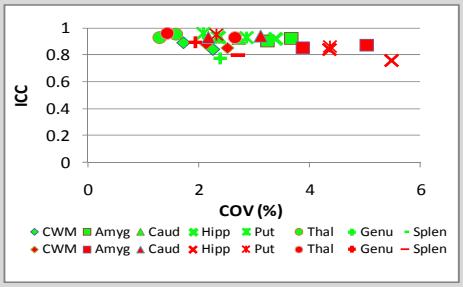

Fig2.Scatterplot of ICC and COV forautomated method (green) and manual method (red)

Table 1. ISD using Bland-Altman Analysis (Automated vs. Manual)

	Automated			Manual		
	Mean	95% CI	ISD	Mean	95% CI	ISD
Left amyg	0.53	-0.64, 1.71	1.1	0.19	-1.44, 1.82	1.5
Right amyg	0.43	-0.61, 1.47	1	-0.6	-1.9, 0.63	1.2
Left cau	0.66	-0.18, 1.5	0.8	0.93	0.26, 1.6	0.6
Right cau	0.78	0.06, 1.49	0.7	0.13	-0.83, 1.09	0.9
Left put	0.4	-0.5, 1.3	0.8	-0.1	-1.52, 1.29	1.3
Right put	0.31	-0.35, 0.96	0.6	0.13	-0.62, 0.88	0.7
Left thal	0.67	0.12, 1.22	0.5	-0	-0.97, 0.89	0.9
Right thal	0.88	0.43, 1.33	0.4	-0.7	-1.16, -0.14	0.5
Left hipp	-0.2	-1.26, 0.82	1	-0.9	-2.67, 0.81	1.6
Right hipp	0.09	-0.73, 0.92	0.8	0.37	-1, 1.74	1.3
Left WM	0.24	-0.62, 1.1	0.8	0.05	-0.76, 0.85	0.8
Right WM	0.39	-0.27, 1.05	0.6	0.48	-0.46, 1.43	0.9
Genu	0.63	-0.38, 1.63	0.9	0.09	-0.69, 0.87	0.7
Splen	0.38	-0.5, 1.26	0.8	0.81	-0.27, 1.9	1

Results: For the automated method, excellent scan-rescan agreement was achieved. In 10 of the 14 studied brain regions, ICCs were above 0.9 (ICC range: 0.77- 0.96); 11 of 14 COV <3% (COV range: 1.3-3.7%); in 12 of the 14 regions ISDs were below 1%. Generally, scan-rescan reliability was slightly higher for the automated method relative to the manual method as indicated by higher ICCs and lower COVs (top left corner of Fig 2). Instrumental variation ranged from 0.42-1.1 for automated measurements and 0.47-1.62 for manual method (Table 1). While the ICCs, COVs and ISDs were superior for the automated method compared to manual measurements, both demonstrated high agreement for quantitative measurements between scanning sessions.

Discussion: MTR measurements derived from high-resolution MT images at 3T achieved good to excellent reliability, with the generally automated method being superior with higher ICC and lower COV and ISD compared to the manual method. The ISD for the automated method was comparable to previous reports at 1.5T that primarily focused on white matter regions. In this investigation, reliable and reproducible MTR measurements were obtained not only for white matter regions, but also for basal ganglia and subcortical gray matter, which are responsible for manifesting neurological diseases such as Alzheimer's and Parkinson's. The availability of automated methods for quantifying localized pathology has potential to accelerate progress in clinical diagnosis, monitoring and treatment of neurodegenerative disease.

References:

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