Reliability and Reproducibility of High Resolution Magnetization Transfer Imaging on 3T

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Introduction: Magnetization transfer (MT) imaging is a quantitative approach that is sensitive to subtle or occult abnormalities in brain tissue. To monitor chronic neurological diseases (e.g. Multiple Sclerosis or Alzheimer's disease), however, requires serial measurements with good reproducibility and precision. Automated methods that reduce post-processing demands and operator bias would be of considerable clinical benefit. This investigation evaluated the reliability and reproducibility of high resolution quantitative MT at 3 Tesla (3T). Both manually defined, as well as fully automated methods, were used to extract MT measurements for brain regions of interest.

Method and Materials:

MR Image Acquisition: 9 healthy volunteers (7 males of 22 – 59 years and 2 females of 38-40 years) were scanned twice in an interval of one week. Images were acquired using a 3T General Electric HDx system (Waukesha, WI). High resolution MT images were obtained using a three-dimensional gradient echo sequence (TR/TE/FA 34-35ms / 6-8 ms/ 12°. Spatial resolution = 0.93x0.93x 0.9 ~ 1.3 mm^3). Saturation pulse (with and without MT) was applied for 16 ms, 1200 Hz offset from water resonance. Structural SPGR-IR was obtained with spatial resolution identical to MT.

Quantitative Analysis of MTR:

***Manual measurements*:** Magnetization transfer ratio (MTR) maps were generated using standard equations on a GE AW Workstation (General Electric, Milwaukee, WI). ROIs (30 ~ 43mm^2) were manually and independently placed by two separate operators. The same procedures were repeated a week later to assess inter- and intra-operator variation associated with manual measurements.

***Automated measurements*:** Whole brain pixel-by-pixel MTR maps were constructed on a Linux workstation using custom software. Automated segmentation was implemented on the structural MR using FreeSurfer (1). Co-registration was applied to the structural MR and MT images. Volumetric segmentation masks for putamen (put), hippocampus (Hipp), thalamus (Thal), genu and splenium (Splen) were projected onto the MTR maps to extract measurements. This procedure was fully automated and required no operator intervention.

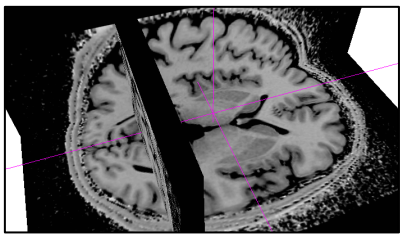

Fig1. High resolution MTR maps displayed on Axial, Coronal and Sagital planes.

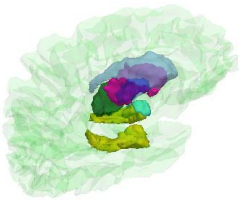

Fig2. 3D rendering of segmented brain masks. Color code: basal ganglia = blue and magenta. Hippocampus = yellow. White matter = green.

Statistical Analysis: For each anatomical region, the limit of agreement between time points 1 and 2 was calculated using the Bland-Altman method (2). A paired Student's *t* test was used to assess the difference between the bivariate measurements at the two time points. Cronbach's alpha was calculated to evaluate the reliability coefficient (RC), together with the coefficient of variation (CV) (CV=SD/mean, in %) for the reproducibility and reported according to (3). Inter-rater and intra-rater variability for the manual method was estimated with intraclass coefficients (ICC).

Results: For both the automated and manual method, the Bland-Altman method demonstrated moderate to high agreement for quantitative measurements between scanning sessions (Table 1). There were no statistically significant differences over two time points. RC values close to or above 0.7 with low CVs of less than 10% (six of eight studied brain regions < 2%) were observed for all studied brain regions (Fig 3). Compared to the manual method, the automated method was generally superior with higher RC and lower CV across brain regions (Fig 3) (2). For manual measurements, ICCs ranged from -0.01 to 0.95 for inter-rater variation and -0.02 to 0.95 for intra-rater variation (Table 2); agreement was low for both sides of thalamus.

Table 1: Bland-Altman Agreement of MTR of Two Time Points

Brain Region	AUTOMATIC			MANUAL		
	mean±sd	limit of agreement		limit of agreement		mean±sd
		L	U	L	U	
Genu	77.6±0.2	-1.6	2.1	-1.1	2.0	77.1±0.3
Splen	74.4±0	-2	1.6	-1.8	2.6	72.6±0.3
l - Hipp	51.67±0.5	-5.6	6.2	-4.3	4.8	51.6±0.2
l - Put	61.6±0.2	-1.8	2.7	-2.5	3.0	62.1±0.1
l - Thal	64.4±0.1	-1.9	2.4	-2.8	3.2	63.3±0.1
r - Hipp	52.0±0.9	-7	8.7	-5.0	4.4	51.5±0.2
r - Put	62±0.2	-2.2	3.1	-2.9	2.8	62.8±0.0
r - Thal	64.5±0.3	-2	2.6	-4.9	3.6	62.5±0.5

Note: l= left; r = right; L= lower; U=upper

Reproducibility and Reliability of Automated and Manual Measurements

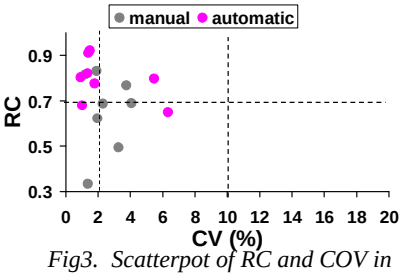

Fig3. Scatterpot of RC and COV in different brain regions

Table 2: Inter-rater and Intra-rater Reliability (Manual Method)

Brain Region	ICC (inter-rater)	ICC (intra-rater)
Genu	0.72	0.88
Splen	0.39	0.60
L - Hipp	0.67	0.15
L - Put	0.95	0.40
L - Thal	0.14	-0.07
R - Hipp	0.58	0.95
R - Put	0.32	0.44
R - Thal	-0.01	-0.02

Conclusion: These findings indicate good reproducibility for high resolution MT measurements acquired both with manual and automated methods. Automated methods were generally superior with higher RC and lower CV across brain regions. Moreover, this approach completely eliminates measurement variation introduced by the operator. These findings support the feasibility of high resolution MT for longitudinal MT studies. Reliable and reproducible measurements were obtained not only for white matter regions, but also for functionally eloquent basal ganglia gray matter regions. In particular, the availability of automated methods for quantifying localized pathology promises to accelerate progress in clinical diagnosis, monitoring and treatment of neurological disease

Reference: **1)** Fischl, B et al. Neuron 2002; 33:341. **2)** Bland JM et al. *Lancet* 1986; I: 307. **3)** Vavasour IM et al., NeuroImage 2006; 32:637.